**SR-B1 and Atherosclerotic Cardiovascular Disease: A Pivotal Role of Macrophage SR-B1 in Atherogenesis**

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**Abstract.**

**Purpose of review.** Scavenger receptor class B type 1 (SR-B1) promotes atheroprotection through its role in high-density lipoprotein (HDL) metabolism and reverse cholesterol transport in the liver. However, evidence suggests that SR-B1 may impact atherosclerosis through non-hepatic mechanisms.

**Recent findings.** Recent studies have brought to light various mechanisms by which SR-B1 affects lesional macrophage function and protects against atherosclerosis. In early atherosclerotic lesions when efferocytosis is efficient, SR-B1 promotes free cholesterol-induced apoptosis of macrophages through the control of the apoptosis inhibitor of macrophage (AIM), beyond its role in cholesterol efflux. At more advanced stages, macrophage SR-B1 binds and favors the removal of apoptotic cells. SR-B1 also participates in the induction of autophagy which limits necrotic core formation and increases plaque stability.

**Summary.** These studies shed new light on the atheroprotective role of SR-B1 by pointing out its pivotal function in macrophages during atherogenesis as a function of lesion stages. These new findings suggest that macrophage SR-B1 is a therapeutic target in cardiovascular disease.

**Keywords:** SR-B1, macrophage, cholesterol, apoptosis, atherosclerosis

**Introduction.**

According to the World Health Organization (WHO), cardiovascular disease (CVD) remains the leading cause of mortality and morbidity worldwide. The inverse correlation of circulating high-density lipoprotein (HDL) levels with the risk of atherosclerotic cardiovascular disease (ASCVD) was first reported in the late seventies (1,2) and since confirmed by numerous epidemiological studies. Patients with low plasma concentrations of HDL cholesterol (HDL-C) exhibit a high risk of ASCVD that may reflect the protective biological activities of HDL particles (3). Among them is the capacity of HDL to promote reverse cholesterol transport (RCT) through which cholesterol returns from peripheral tissues to the liver for elimination. This RCT pathway was proposed to underly the atheroprotective role of HDL (4). However, intervention studies aimed at raising HDL-C levels (5,6), infusion of recombinant HDL (7,8) and Mendelian randomization studies (9) do not support a causal role of HDL in CVD. Epidemiological studies also pointed to a U-shaped relationship between HDL-C and CVD where very high HDL-C plasma concentrations were associated with an increased risk of CVD and mortality (10,11). Such results have prompted questions about the role of HDL in lipid metabolism and CVD (12).

From biogenesis at liver and intestinal sites, remodeling in the vascular compartment and recycling and catabolism by the kidney, numerous enzymes and receptors are involved in HDL metabolism ( ). In this context, the scavenger receptor class B type 1 (SR-B1) is a physiological HDL receptor (13) that plays a pivotal role in HDL metabolism and signaling (14); however, its role in CVD may be more complex than anticipated by earlier studies ( ).

**A brief overview of SR-B1 structure and regulation.**

SR-B1 is a member of the class B scavenger receptor family that includes CD36 (or SCARB3) and lysosomal integral membrane protein 2 (LIMP-2). An SR-B2 isoform of the receptor has been described with a divergent cytoplasmic tail due to alternative splicing (15). Human SR-B1 is encoded by the *SCARB1* gene on chromosome 12 which contains 13 exons and 12 introns (16) and generates a protein of molecular mass 82 KDa following post-translational modifications. SR-B1 protein is composed of two short intracellular domains at the N- and C-extremities, two transmembrane domains and a large extracellular domain forming an ectodomain responsible for the binding of HDL. Importantly, the C-terminal cytosolic domain contains motifs involved in SR-B1 expression (PDZ binding domain) and activity (SIK-1 binding domain) (14). Although SR-B1 is expressed in numerous cell types, the highest expression is found in the liver, ovary and adrenal glands. Regulation of SR-B1 expression is tissue-dependent and mainly involves trophic hormones such as adrenocorticotropin in adrenal glands, anterior pituitary hormones in the ovary, and biliary acids in the liver (14). It is noteworthy that in the context of ASCVD, expression of SR-B1 via the regulatory binding proteins SREBP-1a (17), SREBP-2 (18) and LXRα/β is highly regulated by cholesterol LRH-1 (19) and PPAR agonists (20) in the liver and macrophages.

**SR-B1 is a major player in cholesterol homeostasis and atherosclerosis.**

The SR-B1 receptor plays a major role in HDL metabolism by mediating both the uptake and efflux of cholesterol between cells and large mature HDL. Importantly, expression of SR-B1 in hepatocytes promotes the selective uptake of cholesteryl esters from HDL (21,22) and RCT (23) and contributes to the optimal recycling of circulatory HDL. Such a function was recently proposed to involve the multimerization of SR-B1 into large metastable clusters at the plasma membrane, thereby evading endocytic pathways in a process requiring a C-terminal leucine zipper motif within SR-B1 (24). In genetically-modified mouse models, overexpression of SR-B1 in hepatocytes was accompanied by reduced plasma HDL-C (25,26) and decreased atherosclerosis (25). Conversely, SR-B1 deficiency in hepatocytes led to the opposite phenotype (27) which recapitulated the detrimental effect of SR-B1 on atherosclerosis when its expression in the whole body was attenuated or ablated (27–30). In humans, the importance of SR-B1 in HDL metabolism was corroborated with the identification of the functional *SCARB1* variants P297S and P376L that exhibited decreased HDL cholesterol uptake in hepatocytes and increased HDL-C in plasma of carriers of the mutations (31,32). Analysis of carotid artery intima-media thickness in a small group of heterozygous carriers of the P297S mutation revealed no difference compared to noncarriers within the family. Rare *SCARB1* variants were also not associated with coronary artery disease (CAD) despite elevated HDL-C levels in the relatively homogeneous population of Iceland (33). However, an association between P376L carrier status and coronary heart disease (CHD) in 137,995 individuals from the CARDIoGRAM Exome and the CHD Exome+ Consortia revealed that carriers of this variant display elevated HDL-C concentrations and an increased risk of CHD (OR: 1.79) (32). These findings support epidemiological studies linking extremely high HDL-C with CHD risk and mouse model studies using genetically-modified SR-B1. However, they must be interpreted with caution because of the very low frequency of the P376L variant in both healthy controls (n=52) and CHD cases (n=34) detected in this meta-analysis ( ). It must also be kept in mind that mouse and genetic studies pointed out that SR-B1 not only plays a role in HDL metabolism. It also participates in the clearance of apoB-containing lipoproteins which may contribute to the relationship between SR-B1 and CAD (34). Such a hypothesis is supported by recent genome-wide association studies reporting associations between the *SCARB1* locus and CAD risk independently of HDL-C (35,36).

Interestingly, study of *SCARB1* variants equally highlighted a potential impact of SR-B1 in platelet activation and glucocorticoid production. Altered platelet function and decreased adrenal steroidogenesis were also reported in carriers of the P297S mutation (31). In support of these studies, a critical function of SR-B1 in providing lipoprotein-derived cholesterol for glucocorticoid synthesis in response to stress was clearly demonstrated in mice (37). In addition to the pivotal role of SR-B1 in the cellular import of HDL-C, a recent study proposed that large HDL enriched in free cholesterol (FC) resulting from SR-B1 deficiency may drive FC delivery into tissues. This mechanism may equally contribute to their dysfunction in the absence of SR-B1 (38).

**SR-B1 in endothelial cells and atherosclerosis.**

Beyond the importance of liver SR-B1 in HDL metabolism, studies have highlighted the contribution of SR-B1 to the protective action of HDL on the vascular endothelium by propagating HDL signaling which stimulates endothelial nitric oxide synthase (39). HDL-mediated intracellular signaling relies on SR-B1 receptor interaction with plasma membrane cholesterol via the SR-B1 C-terminal transmembrane domain (40). Interestingly, the contribution of endothelial SR-B1 in promoting HDL-mediated neuroprotection was recently demonstrated in the context of acute ischemic stroke (41). SR-B1 may also act as a transporter in endothelial cells to facilitate the entry of lipoproteins such as HDL and LDL into the subendothelial space by transcytosis (42,43). Notably, a recent study demonstrated that SR-B1 binds LDL and drives their transcytosis across aortic endothelial cells by a mechanism that requires binding of dedicator of cytokinesis 4 (DOCK4) to SR-B1 and activation of the Rho GTPase ras-related C3 botulinum toxin substrate 1 (RAC1). This SR-B1-mediated active transport of LDL to the artery wall promotes atherosclerosis and is the first demonstration of a pro-atherogenic activity for the receptor (43).

**SR-B1 in hematopoietic cells and atherosclerosis.**

Comparison of liver-specific *srb1* KO mice to fully-deficient mice demonstrated that, in addition to its major atheroprotective role in liver, SR-B1 exerts an anti-atherogenic role in extrahepatic tissues (27). This is in agreement with earlier studies demonstrating increased atherosclerosis in mice transplanted with *Srb1* KO bone marrow (BM) (44–47). Importantly, modulation of atherosclerosis consecutive to the lack of SR-B1 in hematopoietic cells was independent of any alteration of plasma HDL- or total cholesterol levels. Although these studies concluded that the expression of SR-B1 in macrophage underlies the atheroprotective role of SR-B1 in BM-derived cells, the final demonstration of a critical role of SR-B1 in macrophages was brought only recently by Galle-Treger *et al*. (48) through transplantation studies using BM from *Lysm*-Cre x *Srb1*fl/fl mice. Noteworthy, earlier studies have suggested that SR-B1 could also contribute to atheroprotection by promoting HDL-mediated control of the proliferation and differentiation of hematopoietic stem/progenitor cells in the BM, thus limiting leukocytosis and inflammation (49).

**SR-B1 in macrophages and atherosclerosis.**

**Cholesterol efflux and RCT.**

Among immune cells involved in atherosclerosis, macrophages exert a central role in the initiation and progression of disease (50). One atheroprotective function of HDL is the capacity of plaque macrophages to get rid of excess cholesterol by promoting efflux to HDL for elimination through RCT. Thus, *ex vivo* evaluation of the capacity of HDL from patients to facilitate macrophage cholesterol efflux is inversely associated with atherosclerosis (51), incident cardiovascular events (52) and mortality (53). SR-B1 is expressed in tissue macrophages and specifically in atherosclerotic lesions in humans (20). Because it promotes cholesterol efflux to HDL, it was initially proposed that SR-B1 expression in macrophages could enhance RCT resulting in reduced foam cell and plaque formation. Cholesterol efflux from human macrophages to HDL *in vitro* was reduced by antibody-mediated neutralization of SR-B1 (54) or when macrophages isolated from carriers and non-carriers of the dysfunctional *SCARB1* P297S variant were compared (31). In mice, however, the importance of macrophage SR-B1 in mediating cholesterol efflux to HDL (45,55), promoting macrophage foam cell formation (47,48,56) or participating in *in vivo* RCT (57,58) is unclear due to conflicting results. It is noteworthy that the combined deletion of *Sr-b1* and genes known to contribute to cholesterol efflux, such as *ATP binding cassette A1* *(Abca1)* or *apolipoprotein E (ApoE),* dramatically enhanced the formation of macrophage foam cells (47,59). In double SR-B1/APOE knockout (KO) mice, dyslipidemia and altered cholesterol mobilization, with an accumulation of FC into lysosomes due to SR-B1 deficiency, contribute to cholesterol accumulation in macrophages (59). In double ABCA1/SR-B1 KO mice, massive macrophage lipid-loading occurs even under hypocholesterolemia in these animals (47). Interestingly, Liu et al (38) recently reported that FC-rich HDL particles generated in SR-B1 deficient mice also favor free cholesterol accumulation in macrophages.

**Apoptosis.**

Apoptosis of macrophages is a critical event during atherogenesis with divergent effects on the progression of the pathology. Macrophage apoptosis is proposed to be atheroprotective in early lesions, whereas it favors atherosclerosis development at more advanced stages (60). The specific deletion of macrophage SR-B1 in two different atherosclerotic mouse models recently revealed a marked reduction in apoptotic macrophages in developing aortic lesions (48). Mechanistically, Galle-Treger *et al.* observed that SR-B1-deficient macrophages were less susceptible to apoptosis induced by free cholesterol loading compared to control macrophages with reduced activation of p38MAPK and STAT1 which are critical players in free cholesterol-driven macrophage apoptosis. SR-B1-deficient macrophage resistance to apoptosis was associated with the induction of the anti-apoptotic factor AIM (CD5L, Spα, Api6)(61) in a STAT3-dependent manner. AIM is a member of the scavenger receptor cysteine-rich superfamily (SRCR-SF)(48). Similar induction of AIM was observed in atherosclerotic macrophages ( ). Interestingly, reduction of macrophage apoptosis with increased atherosclerosis in macrophage SR-B1-deficient mouse models did not change the extent of plaque necrosis (48). Altogether, these results suggested a pro-survival effect of AIM in SR-B1-deficient macrophages leading to increased plaque cellularity and early expansion of lesions in the context of efficient efferocytosis. Other mechanisms may contribute to the pro-apoptotic role of SR-B1 during atherogenesis. Indeed, SR-B1 could also contribute to a defect in the normal clearance of apoptotic cells by macrophages (efferocytosis) (46) and regulate autophagy (56) as recently reported in advanced atherosclerotic lesions (46,56).

**Efferocytosis**

Efferocytosis is an important driver of plaque necrotic core formation in advanced atherosclerotic lesions because it alleviates the necrosis of apoptotic cells including macrophages (62). In this context, Tao *et al.* suggested that macrophage SR-B1 could influence efferocytosis (46). They reported that SR-B1 bound to phosphatidylserine (PS) at the surface of apoptotic cells resulting in the recruitment and phosphorylation of the Src tyrosine kinase and the downstream activation of phosphatidylinositol 3 kinase (PI3K)/Rac1 GTPase leading to membrane ruffling. In *in vitro* and *in vivo* assays, macrophage SR-B1 deficiency was associated with defective efferocytosis. Hematopoietic SR-B1 deficiency was also associated with an increased number of apoptotic cells, less events of engulfment of apoptotic cells by macrophages and more necrosis in advanced atherosclerotic lesions of BM transplanted *Ldlr*-/- mice ( ). These effects were reinforced when double SR-B1 and ApoE deficient hematopoietic cells were used. The combined deficiencies were associated with evidence of plaque instability resulting from a reduction of the collagen content and fibrous cap thickness (46). Altogether, SR-BI appears to play an atheroprotective role by promoting efferocytosis in late-stage lesions. The results cannot exclude, however, that accelerated plaque development in macrophage SR-B1-deficient atherosclerotic mice (48) also contributed to impaired efferocytosis because efferocytosis is defective in advanced atherosclerosis (63,64).

**Autophagy.**

The accumulation of neutral lipids, including the esterified form of cholesterol within lipid droplets in macrophages, was proposed to induce autophagy and promote free cholesterol via its efflux from autophagosomes to lysosomes (65). Although the relevance of this finding to atherosclerosis has not been determined, mice with deficient autophagy in macrophages displayed increased plaque necrosis, macrophage apoptosis and defective efferocytosis (66). In this context, the regulation of macrophage autophagy by SR-B1 was recently suggested to contribute to its atheroprotective properties (56). Thus, deletion of SR-B1 in macrophages resulted in impairment of the peroxisome proliferator-activated receptor alpha (PPARα)-induced expression of transcription factor EB (TFEB), a master regulator of genes involved in lysosomal biogenesis and autophagy ( ). Notably, expression of the autophagy genes VPS34 and Beclin-1was reduced in SR-B1-deficient macrophages and led to defective autophagy, the latter being rescued by the overexpression of TFEB or VPS34. The role of SR-B1 in autophagy was further shown to involve the recruitment of the VPS34 complex and Barkor in cholesterol domains in autophagosomes (56). The impact of defective autophagy on cholesterol efflux in SR-B1-deficient macrophages was not investigated, however. Finally, reduced signs of autophagy, including reduced VPS34 activity, in advanced atherosclerotic lesions of mice with a hematopoietic deletion of SR-B1 suggest that SR-B1 may actively contribute to the induction of autophagy at later stages of the disease.

**Conclusions.**

Beyond the well-described atheroprotective role of liver SR-B1 on HDL metabolism and RCT (14), recent studies have brought to light diverse non-hepatic mechanisms by which SR-B1 may impact atherosclerosis. Early comparison of liver SR-B1-deficient to fully SR-B1-deficient mice demonstrated that SR-B1 globally exerts an anti-atherogenic role in extrahepatic tissues (27). However, the recent discovery that SR-B1 acts in endothelial cells as a transporter facilitating lipoprotein transcytosis revealed that it could also be pro-atherogenic (43). This deleterious role opposes those of SR-B1 in the macrophage. New findings support a model in which macrophage SR-B1 exerts several protective activities during atherogenesis as a function of the lesion stage. In the early development of atherosclerosis, SR-B1 could promote macrophage cholesterol efflux and RCT resulting in reduced macrophage foam cell formation. Importantly, SR-B1 could favor macrophage apoptosis in response to the cholesterol burden to limit plaque growth. In advanced lesions, SR-B1 could limit the formation of the necrotic core and promote plaque stability via the clearance of apoptotic cells **(Figure 1)**. These studies suggest that macrophage SR-B1 is a potential therapeutic target in CVD. Further investigations are needed to identify pharmacological tools that induce SR-B1 expression and activity in macrophages in atherosclerotic lesions. The ongoing development of macrophage-targeted nanomedicine could be of precious help for achieving this goal (67).

**Key points**.

* Both hepatic and extrahepatic SR-B1 serve major atheroprotective roles.
* Macrophage SR-B1 exerts several protective activities during atherogenesis as a function of the lesion stage.
* Pharmacological raise of SR-B1 expression and/or activity in macrophages in atherosclerotic lesions is a potential therapeutic target in CVD.

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**This study first brought to light the atheroprotective role of both hepatic and extrahepatic SR-B1.**

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**Figure titles and legends.**

**Figure 1. Protective activities of macrophage SR-B1 during atherogenesis as a function of the lesion stage.** Beyond theatheroprotective role of liver SR-B1 on HDL metabolism and RCT, non-hepatic SR-B1 contributes to atherogenesis through several activities. SR-B1 alleviates leukocytosis and inflammation by promoting HDL-mediated control of the proliferation and differentiation of hematopoietic stem/progenitor cells in the bone marrow. At the vascular endothelium level, SR-B1 exerts both anti- and pro-atherogenic activities by facilitating transcytosis of LDL and maintaining vascular homeostasis through NO production, respectively. At the early stage of atherosclerosis development, SR-B1 promotes macrophage cholesterol efflux to HDL and RCT and favors macrophage apoptosis in an AIM-dependent mechanism resulting in reducing foam cell formation and plaque macrophage content. At later stages of atherosclerosis development, macrophage SR-B1 contributes to efferocytosis through activation of the PI3K/Rac1 pathway. SR-B1 also participates in TFEB and VPS34-mediated autophagy that limits the formation of the necrotic core and favors plaque stability.

AIM, apoptosis inhibitor of macrophage; HDL, high-density lipoprotein; HSPC, hematopoietic stem/progenitor cells; LDL, low-density lipoprotein; NO, nitric oxide; PI3K, phosphoinositide 3 kinase; Rac1, ras-related C3 botulinum toxin substrate 1; SR-B1, scavenger receptor class B type 1; TFEB, transcription factor EB. Cholesterol.