Cholesterol and phospholipid transporters in atherosclerotic lesion development

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Scavenger receptor BI and ATP-Binding cassette transporter A1 in reverse cholesterol transport and atherosclerosis

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Abstract

Scavenger receptor class B type I (SR-BI) and ATP-binding cassette transporter A1 (ABCA1) are expressed both in macrophages and in the liver, implicating an important role for these transporters in the different stages of reverse cholesterol transport. This review focuses on the current view on the role of SR-BI and ABCA1 in reverse cholesterol transport and the implications for atherosclerotic lesion development.

Recent findings

Recent studies indicate that hepatic expression of ABCA1 and SR-BI is important for the generation of nascent HDL and the delivery of HDL cholesteryl esters to the liver, respectively. Macrophage SR-BI and ABCA1 do not significantly contribute to circulating HDL levels. However, the perpetual cycle of HDL lipidation and delipidation by the liver ensures the availability of acceptors for cholesterol efflux to maintain cholesterol homeostasis in macrophages of the arterial wall and reduce the atherosclerotic risk.

In addition, evidence for a new role for hepatic SR-BI, in addition to its established role in the selective uptake of HDL cholesteryl esters, in facilitating postprandial lipid metabolism has been provided recently. Furthermore, VLDL particle secretion by the liver is dependent on ABCA1-mediated nascent HDL formation. Thus, remnant and HDL metabolism are more intertwined at the level of the liver than has been anticipated until now.

Summary

Recent advances in the understanding of the role of ABCA1 and SR-BI in HDL metabolism and their atheroprotective properties indicate an important potential of modulating ABCA1 and SR-BI expression in both arterial wall macrophages and the liver for the treatment of atherosclerotic coronary artery disease.

Introduction

Atherosclerotic cardiovascular disease is the major cause of morbidity and mortality worldwide [1]. A pathological hallmark of atherosclerosis is the excessive accumulation of cholesterol by macrophages leading to their transformation into foam cells [2]. Current therapeutic strategies to prevent atherosclerosis are primarily based on the use of statins, inhibitors of the novo cholesterol synthesis, that decrease serum low-density lipoprotein (LDL) cholesterol levels [3,4]. Despite the proven effectiveness of statins and their widespread use, the incidence of cardiovascular disease still remains high, indicating that there is an important need for new therapies. While LDL cholesterol levels are positively correlated with atherosclerosis, numerous epidemiological studies have established an inverse correlation between the risk for atherosclerosis and high-density lipoprotein (HDL) cholesterol levels [5-7]. Several mechanisms have been proposed by which HDL inhibits the development and progression of atherosclerosis, including protection against oxidative damage, inhibition of endothelial dysfunction, and anti-inflammatory effects. The most important atheroprotective function, however, is its ability to catalyze reverse cholesterol transport, a process that describes the HDL-mediated removal of excess cholesterol from peripheral tissues, including macrophages in the arterial wall, and subsequent delivery to the liver for biliary excretion. The understanding of the process of reverse cholesterol transport and the molecular mechanisms that control serum HDL cholesterol levels have been dramatically increased by the discovery of scavenger receptor BI (SR-BI) and ATP-binding cassette transporter A1 (ABCA1). In this review we will focus on the current view of the role of SR-BI and ABCA1 in reverse cholesterol transport and the implications for atherosclerosis.

Scavenger receptor BI and ATP-binding cassette transporter A1

SR-BI is a 509 amino acid cell surface glycoprotein with a molecular mass of 82-kDa [8,9]. Its predicted secondary structure is comprised of two transmembrane and two cytoplasmic domains as well as a large extra cellular loop containing several N-glycosylation sites [10]. SR-BI is highly conserved in evolution and is expressed in various mammalian tissues and cells, including brain, kidney, intestine, heart, placenta, macrophages, endothelial cells, smooth muscle cells, and various epithelial cells. The highest expression of SR-BI, however is found in organs with critical roles in cholesterol metabolism (liver) and steroidogenesis (adrenal, ovary, testis) [9,11,12]. Distinct binding sites on SR-BI have been implicated in the

binding of a wide array of ligands, including anionic phospholipids [13], advanced glycation end-products [14], apoptotic cells [15], and native and modified lipoproteins [16-19].
SR-BI mediates the selective uptake of cholesteryl esters from HDL by cells by a process in which the cholesteryl esters are internalized without the net internalization and degradation of the lipoprotein itself [reviewed in 20]. The exact cellular mechanisms for selective uptake of cholesteryl esters, however, are largely unknown. SR-BI reconstituted into liposomes mediates high affinity lipoprotein binding and selective cholesterol uptake, indicating that selective uptake is an intrinsic capacity of the receptor and does not require specific cellular structures or compartments [21]. Alternatively, several recent studies have indicated a so-called retro-endocytosis pathway, which involves the holo-particle uptake of HDL followed by re-secretion of cholesteryl ester-poor HDL leading to the net uptake of lipids. [22-24]. The relative contribution of both pathways, however, is currently unknown. In addition to its role in the selective uptake of HDL cholesteryl esters, SR-BI stimulates the bi-directional flux of free cholesterol between cells and HDL and the rate of cholesterol efflux from various cell types correlates with the expression of SR-BI [25-27].
ABCA1 is a 2,261-amino acid, 240-kDa protein belonging to a large family of conserved transmembrane proteins that use ATP as an energy source to transport a wide variety of substrates across cellular membranes [28]. ABC transporters typically consist of two 6-helix transmembrane domains that serve as a pathway for the translocation of substrates across membranes and two nucleotide-binding domains that bind ATP and provide the energy for substrate transport [29,30]. In contrast to SR-BI, which binds mature HDL, ABCA1 interacts preferentially with lipid-poor apoA-I. Binding of apoA-I to the extracellular domain of ABCA1 results in the lipidation of apoA-I and the formation of nascent HDL. Lipidation of apoA-I by the transfer of phospholipids and cholesterol has been suggested to reduce the binding affinity to ABCA1, resulting in the release of the lipidated apoA-I [31]. However, Fitzgerald and colleagues recently demonstrated that a mutant form of ABCA1 (W590S) that avidly binds apoA-I but fails to promote lipid efflux to apoA-I, released apoA-I with the same kinetics as wild-type ABCA1, indicating that release of apoA-I from ABCA1 is independent of lipid transfer [32].
In addition to apoA-I also other apolipoproteins with an amphipathic helical motif, including apoA-II, apoC-I, apoC-II, apoC-III, and apoE, efficiently induce lipid efflux [32-34]. The exact molecular interaction between ABCA1 and the amphipathic apolipoprotein acceptors and the mechanism of lipidation are subject of intensive investigation. According to one model ABCA1 is proposed to flip phospholipids to the outer leaflet of the plasma membrane

that are subsequent microsolubilized by apoA-I [35,36]. On the other hand several lines of evidence suggest that ABCA1 acts as a receptor for apoA-I that induces the transfer of cholesterol and phospholipids upon binding of the ligand to its receptor [34,37,38]. In addition, also a hybrid model has been proposed in which apoA-I first interacts with the lipid bilayer and then through lateral diffusion subsequently forms a complex with ABCA1 [39]. Interestingly, recently Denis et al. provided evidence that the majority of ABCA1 exists as a tetramer that binds apoA-I and that the formed nascent lipoproteins contain at least four molecules of apoA-I [40].

ABCA1 is a ubiquitously expressed protein, with highest expression levels in placenta, fetal tissues, lung, adrenal glands, brain, and liver [41]. In addition, ABCA1 is highly expressed in macrophages and its expression is stimulated by cholesterol loading. The fact that SR-BI and ABCA1 are expressed both in macrophages and in the liver implicates an important role for these transporters in the different stages of reverse cholesterol transport from the generation of nascent HDL, efflux of cholesterol from arterial wall macrophages, to the delivery of HDL cholesteryl esters to the liver for excretion into the bile.

SR-BI and Lipoprotein Metabolism

The first direct evidence that SR-BI plays an important physiological role in HDL metabolism was obtained from studies using genetically-engineered mice. Adenovirus-mediated hepatic over-expression of SR-BI resulted in the virtual disappearance of plasma HDL and a substantial increase in biliary cholesterol [42]. A similar decrease in plasma HDL cholesterol levels was found in transgenic mice over-expressing SR-BI under control of the apoA-I promoter [43]. These studies indicated the importance of SR-BI in the liver for HDL metabolism and cholesterol secretion into the bile. Studies using transgenic mice with liver-esters by the liver as compared to non-transgenic controls [44,45]. In contrast, mice with an attenuated expression of SR-BI (SR-BIatt mice) due to a mutation in the promoter for SR-BI, displayed a decreased hepatic uptake of HDL cholesteryl esters [46]. Conclusive evidence for the role of SR-BI in HDL metabolism was provided by the generation of SR-BI knockout mice [47,48]. Complete disruption of SR-BI function resulted in a ~2-fold increase in total plasma cholesterol levels due to the accumulation of abnormally large HDL particles, specific regulators of hepatic cholesterol homeostasis, including HMG-CoA reductase, the LDL not over-expression of SR-BI showed an increased selective uptake of HDL cholesteryl reflecting alter the hepatic cholesterol (ester) content nor did it affect the expression of key impaired

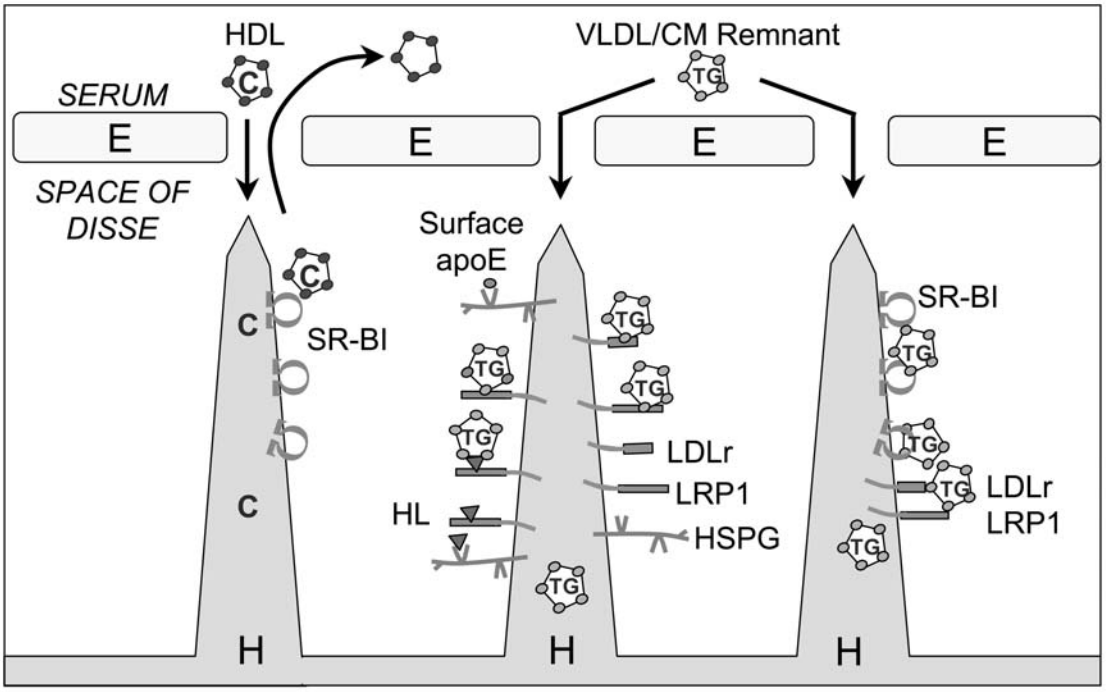

Figure 1. Role of SR-BI in the processing of HDL and remnant lipoproteins by the liver
SR-BI mediates the selective uptake of cholesteryl esters from HDL without net degradation of the HDL particle itself followed by the release of cholesteryl ester-poor HDL (left). VLDL and chylomicron remnants are taken up by the liver via a classical endocytotic pathway, that involves an initial sequestration and capture of step in the space of Disse, followed by internalization via the LDL receptor or the LDL receptor-related protein (LRP1) (middle). Recently also a role for SR-BI in the removal of lipoprotein remnants was established (right). It might be speculated that SR-BI functions in the initial sequestration and capture of remnants whereby the subsequent internalization is exerted by receptor systems-like the LDL receptor or LRP1.

receptor, and cholesterol 7α-hydroxylase. However, SR-BI deficiency did result in an delivery of cholesteryl esters to the liver. Strikingly, SR-BI deficiency did impaired biliary cholesterol secretion [49] and an attenuated expression of ABCG5 and ABCG8, ABC half transporters implicated in the transport of lipids from the liver to the bile [50]. Recent studies in which the uptake of cholesteryl esters from HDL was compared to holo-particle uptake in SR-BI knockout and wild-type mice demonstrated that SR-BI is the sole molecule responsible for the selective uptake of cholesteryl esters from HDL [51, 52].

Interestingly, SR-BI has also been implicated in the clearance of apoB-containing lipoproteins, including LDL and VLDL. In vitro, SR-BI recognizes apoB-containing lipoproteins [15-19] and apoE [53-56], an important ligand for VLDL removal from the circulation. In vivo, transgenic mice over-expressing SR-BI display reduced levels of apoB-containing lipoproteins [44,57] and are not susceptible to the dietary increase in VLDL and LDL levels upon feeding a high-fat/high-cholesterol diet in a heterozygous LDL receptor knockout background [58]. In addition, adenoviral over-expression of SR-BI reduces VLDL

and LDL levels in C57Bl/6 mice [42,59] and reverses fibrate-induced hypercholesterolemia in apoE-/- mice [60]. Conversely, increased levels of LDL cholesterol and apoB protein were observed in LDL receptor knockout mice with attenuated expression of SR-BI on a high-fat/high-cholesterol diet [61]. Furthermore, disruption of the SR-BI gene in apoE-/- mice results in an increase in circulating VLDL and LDL levels [48]. These observations all implicate an important role for SR-BI in the removal of apoB-containing lipoproteins from the circulation. On the other hand, Webb et al. have recently shown that adenoviral over-expression of SR-BI in human apoB transgenic mice [62] and apoE-/- mice [63] does not affect circulating VLDL and LDL levels.

Interestingly, our group recently demonstrated that the postprandial triglyceride response after an intragastric fat-load is higher in the absence of SR-BI [64]. Furthermore, the association of chylomicron-like emulsion particles to freshly isolated hepatocytes is largely reduced in the absence of SR-BI. Thus, also chylomicron metabolism is altered by disruption of SR-BI in mice. Interestingly, consistent with these data, Pérez-Martinez and colleagues have recently suggested a role for CLA-1, the human homologue of SR-BI in postprandial lipoprotein metabolism in [65]. In addition, several studies on common polymorphisms of CLA-1 have been published demonstrating that variants of the SR-BI gene interfere with the metabolism of lipids, including apoB lipoproteins in humans and that the effects may differ in men and women and are affected by age [66-70]. In Fig. 1 a schematic illustration summarizing the role of SR-BI in HDL and remnant metabolism is shown.

SR-BI and Atherosclerosis

Several lines of evidence indicate an anti-atherogenic role for SR-BI in atherogenesis. Hepatic over-expression of SR-BI protects against the development of atherosclerosis [58,59,71]. Interestingly, the expression level of SR-BI is critical for its effect on atherosclerosis susceptibility. If the SR-BI expression level is too high, HDL levels are too low to sustain net cholesterol movement through the reverse cholesterol transport pathway [71]. Conversely, the atheroprotective effects of high HDL levels are lost, if the turnover of HDL cholesterol is impaired as a result of a reduction of SR-BI expression. LDL receptor deficient (LDLr-/-) mice with an attenuated expression of SR-BI are more susceptible to atherosclerotic lesion development [61]. Furthermore, disruption of SR-BI in wild-type [51] as well as in LDLr-/- mice [72] results in a highly increased susceptibility to atherosclerotic lesion development. When cross-bred onto the apoE knockout background, SR-BI-deficiency leads to severe

cardiac dysfunction and premature death [73,74]. By cross-breeding the SR-BIxapoE double knockout mice with RAG2 mice, that lack B and T lymphocytes, Karackattu et al. recently showed that lymphocytes are not required for the rapid onset of coronary artery disease in the SR-BIxapoE double knockout mice [75].

The pro-atherogenic effects of SR-BI deletion is largely attributed to its effects on the uptake of HDL cholesteryl esters by the liver. However, according to the current understanding that SR-BI affects the removal of apoB-containing lipoproteins, disruption of SR-BI also increases the availability of these atherogenic lipoproteins in the arterial wall. Furthermore, SR-BI is expressed in lipid-laden macrophages in human and murine atherosclerotic lesions [76-78]. SR-BI might thus also play an important role locally in the arterial wall. Bone marrow transplantation studies showed that SR-BI on macrophages protects against the development of advanced atherosclerotic lesions in LDLr-/- [72,79] and apoE-/- mice [80]. In contrast, the development of small fatty streak lesions in LDLr-/- is facilitated by macrophage SR-BI [79]. It thus appears that, depending on the stage of lesion development, SR-BI in macrophages is either pro-atherogenic or anti-atherogenic, indicating a unique dual role for SR-BI in the pathogenesis of atherosclerosis. This concept is illustrated in Fig. 2. The unique dual role is probably a direct effect of the finding that SR-BI is a multi-functional, multi-ligand receptor that facilitates the binding of a wide array of native and modified lipoproteins and mediates the bi-directional flux of cholesterol between HDL and cells. Its function in the binding of atherogenic lipoproteins, like native βVLDL and oxidized LDL is expected to induce foam cell formation, while efflux of intracellular cholesterol to HDL will prevent foam cell formation and thus atherosclerotic lesion development.

Although the atheroprotective function of SR-BI has been well established in genetically-engineered mice, the role of CLA-1 in coronary artery disease in humans is still largely unknown. In female patients with premature coronary artery disease an association was found between a combination of two common variants in exons 5 and 8 of the CLA-1 gene with extreme triglyceride:HDL cholesterol ratios [69]. In addition, recently Rodríguez-Esparragón and colleagues showed an association between the CLA-1 exon 8 gene polymorphism and the risk of coronary artery disease [81]. Furthermore, CLA-1 is expressed in macrophage-rich areas of human carotid atherosclerotic lesions [82], suggesting that this scavenger receptor might also play an important role for atherosclerotic lesion development locally in the arterial wall in humans.

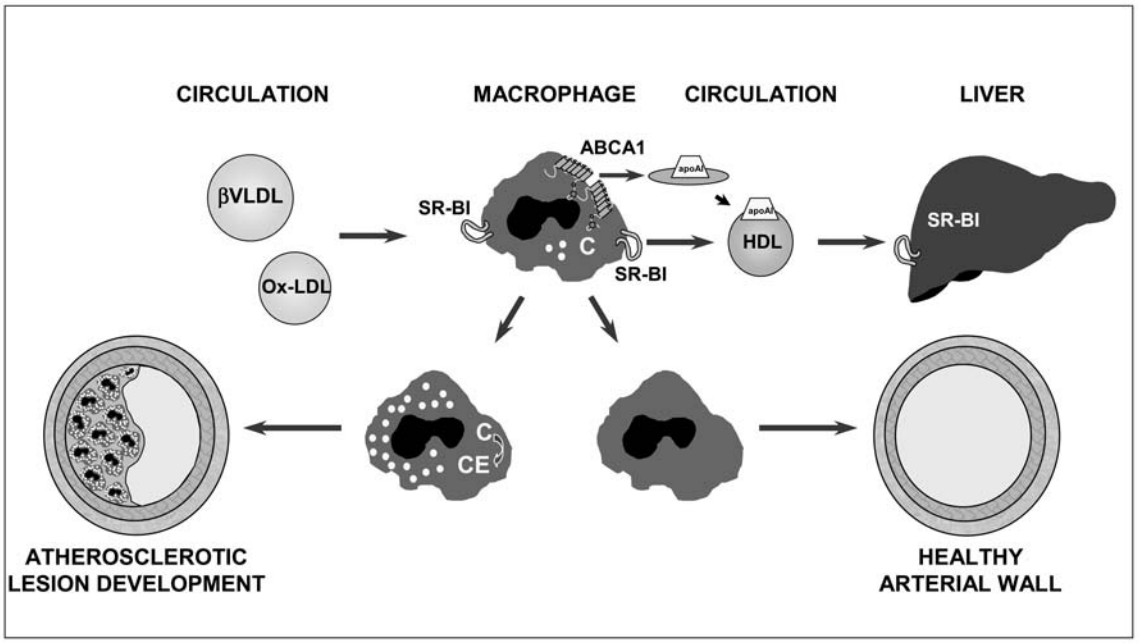

Figure 2. Role of macrophage SR-BI and ABCA1 in atherosclerotic lesion development
Macrophage SR-BI has a unique dual role in atherosclerosis. The development of initial fatty streak lesions is induced by facilitating the uptake of atherogenic lipoproteins like βVLDL and oxidized LDL thereby inducing foam cell formation, whereas at later stages of atherosclerotic lesion development, its function in cholesterol efflux to HDL protects the arterial wall from extensive lipid accumulation. Macrophage ABCA1 protects against atherosclerotic lesion development by mediating the cholesterol efflux to lipid-poor apoA-I.

ABCA1 and Lipoprotein Metabolism

The recognition that mutations in the human ABCA1 gene are the underlying molecular defect in HDL deficiency syndromes such as Tangier disease has contributed substantially to the understanding of the function of ABCA1 as a key transporter in reverse cholesterol transport [83-85]. The importance of ABCA1 in HDL metabolism was further proved in genetically-engineered mice. Targeted disruption of ABCA1 results in a virtual absence of HDL cholesterol [86-88], while ABCA1 over-expression increases HDL levels [89,90]. Since mutations in ABCA1 were recognized to cause rare recessive HDL deficiency syndromes, it has been speculated that sequence variants in ABCA1 might contribute to variations in plasma HDL cholesterol levels in the general population. Recently, Frikke-Schmidt et al. provided evidence from the Copenhagen City Heart Study that at least 10% of individuals with low HDL in the general population are heterozygous for mutations in ABCA1 [91, 92]. This finding is further supported by the data from the population-based Dallas Heart Study and in Canadians with low or high plasma HDL cholesterol levels [93]. According to the classical view of the reverse cholesterol transport pathway, ABCA1 in peripheral cells, including macrophages was presumed to initiate HDL formation by

facilitating the transfer of phospholipids and cholesterol from the plasma membrane to lipid-free apoA-I. However, although total-body ABCA1 deficiency is associated with severe HDL deficiency, specific deletion of ABCA1 in macrophages did not affect circulating HDL cholesterol levels [94,95]. Furthermore, Haghpassand et al. have shown that reconstitution of macrophage ABCA1 expression in ABCA1-deficient mice resulted in only a small but significant increase in apoA-I levels and the appearance of α-migrating HDL [94]. The contribution of macrophage ABCA1 to overall plasma HDL levels is thus small. It must be noted that these studies were performed in the presence of a functional SR-BI in the liver. It is thus possible that cholesteryl esters from freshly lipidated HDL were rapidly removed by the liver via SR-BI, thereby underestimating the role of ABCA1 in the formation of HDL in the periphery. However, serious questions were raised whether the widely held reverse cholesterol transport hypothesis was still valid. The liver secretes lipid-free and lipid-poor apoA-I [96,97] and expresses high levels of ABCA1 protein [41,98,99], suggesting that the liver itself might mediate lipidation of HDL proteins. In a study with isolated primary hepatocytes from wild-type and ABCA1-deficient mice, Kiss et al. showed that hepatocyte expression of ABCA1 is central to the lipidation of newly synthesized apoA-I [100]. In agreement, adenoviral over-expression of ABCA1 in livers of wild-type mice increases HDL production, indicating that the liver can be considered as an important source for the lipidation of HDL in the circulation [101,102]. Recent studies from the lab of J.S. Parks showed that plasma HDL and apoA-I levels are dramatically decreased in mice with a liver-specific deletion of ABCA1 [103, 104]. Conversely, cross-breeding of mice that selectively over-express human ABCA1 in the liver with ABCA1 knockout mice corrected the lipid abnormalities in the ABCA1 knockout mice [105]. Thus the liver indeed seems to play an important role in the lipidation of HDL proteins.

Tangier disease (TD) results in extremely low HDL cholesterol levels as a result of ABCA1 dysfunction. Low HDL cholesterol levels are frequently associated with raised fasting or postprandial triglyceride levels. In a small cohort of patients, Kolovou et al. showed that TD patients display an increased susceptibility to postprandial hypertriglyceridemia [106]. In agreement, Joyce et al. reported that over-expression of human ABCA1 in mice in both liver and macrophages not only induces HDL cholesterol levels, but also results in a marked reduction in VLDL cholesterol levels [107]. Interestingly, Sahoo et al. recently showed, using cultured primary murine hepatocytes, that cholesterol efflux to apoA-I reduced the secretion of triglycerides and apoB from wild-type hepatocytes, but not from hepatocytes lacking ABCA1 [108]. ABCA1-dependent cholesterol mobilization from hepatocytes to apoA-I for

HDL particle formation thus seems to compete for the cholesterol availability for VLDL particle secretion. Previously it has been shown that disruption of ABCA1 in mice does not affect the hepatic cholesterol content or the fecal excretion of sterols [109]. In the light of the recent findings on the link between ABCA1-mediated HDL lipidation and VLDL secretion by the liver, the compensatory effects on the hepatic VLDL secretion in ABCA1 knockout mice should be investigated.

ABCA1 and Atherosclerosis

Heterozygotes for mutations in ABCA1 are significantly at risk for coronary artery disease and ABCA1 gene variations may contribute to the inter-individual variability in atherosclerosis susceptibility in humans [110-116]. The cardioprotective effects of ABCA1 have been confirmed in several animal models. Over-expression of ABCA1 in mice increases serum HDL cholesterol levels and leads to a decreased susceptibility to atherosclerosis in apoE knockout [117] and C57Bl/6 mice [107]. In atherosclerotic lesions, ABCA1 co-localizes with macrophages, indicating that ABCA1 can also affect lesion development independent of effects on HDL cholesterol levels [99]. Indeed, bone marrow transplantation experiments showed that disruption of ABCA1 in macrophages results in a markedly increase in atherosclerotic lesion development [95,118]. Thus, although ABCA1 in macrophages contributes little to the circulating HDL cholesterol levels, ABCA1-dependent cholesterol efflux is a crucial factor in the prevention of excessive cholesterol accumulation in macrophages of the arterial wall and their transformation into foam cells (Fig. 1).
Recently, Albrecht et al. showed that ABCA1 protein levels are reduced in advanced carotid atherosclerotic lesions [119]. Furthermore, in our group it has been found that over-expression of ABCA1 in macrophages could not prevent the initiation of atherosclerosis, but prevented the progression to advanced atherosclerotic plaques [120]. Macrophage ABCA1 is thus an important determinant for the progression of atherosclerosis from initial fatty streaks into advanced lesions, apparently the stage in which endogenous ABCA1 is down-regulated. Stimulation of the expression of macrophage ABCA1 thus forms an attractive therapeutic target for the development of novel therapeutic agents designed to prevent the development of advanced atherosclerotic lesions coronary or cerebral infarction.

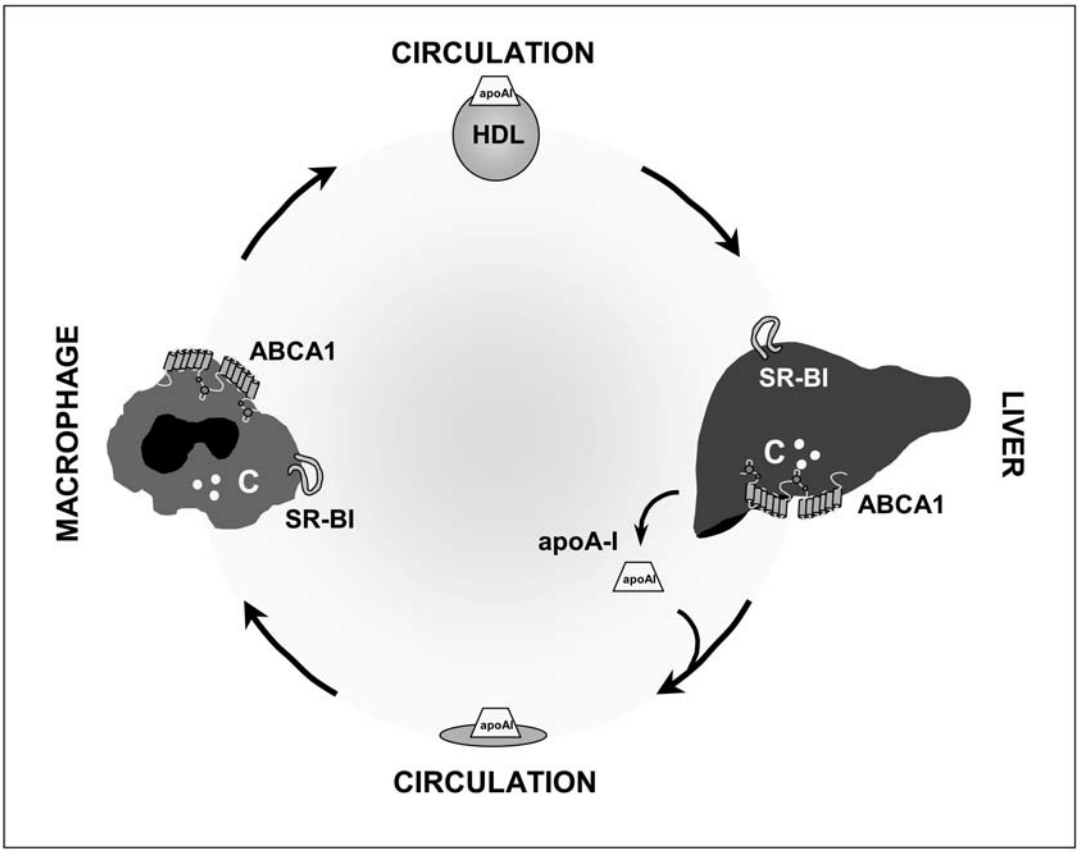

Figure 3. Perpetual cycle of reverse cholesterol transport
Reverse cholesterol transport describes the process in which excess cholesterol from peripheral tissues, including arterial wall macrophages is transported back to the liver. Reverse cholesterol transport, however, does not solely involve unidirectional transport of cholesterol. It is a continuous cholesterol transport cycle in which the liver plays an essential role for the generation of nascent HDL by ABCA1 and the continuous regeneration of lipid-poor HDL by SR-BI, thereby ensuring the availability of acceptors for SR-BI and ABCA1-mediated cholesterol efflux to maintain cholesterol homeostasis in the periphery.

Conclusion

Modulation of SR-BI and ABCA1 expression in liver and macrophages has greatly improved the general understanding of the process of reverse cholesterol transport and the relation between HDL cholesterol levels and atherosclerosis. Importantly, it is not the HDL cholesterol level per se, but rather the kinetics of HDL metabolism in which SR-BI and ABCA1 play a decisive role, that determine the atherosclerotic risk. Furthermore, the process of reverse cholesterol transport should be envisioned as a cycle in which the liver plays an essential role for the generation of nascent HDL by ABCA1 and the continuous regeneration of lipid-poor HDL by SR-BI, thereby ensuring the availability of acceptors for SR-BI and ABCA1-mediated cholesterol efflux to maintain cholesterol homeostasis in the periphery (Figure 3).

In addition, the suggested role for hepatic SR-BI in facilitating postprandial lipid metabolism and the finding that ABCA1-dependent nascent HDL formation competes for the cholesterol availability for VLDL particle secretion, provide new information that remnant and HDL metabolism are intertwined both at receptor level and intracellularly.

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