ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of Gastroenterology®

Indexed and Abstracted in:
Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Digital Object Identifier. ISI, Thomson Reuters, 2009 Impact Factor: 2.092 (33/65 Gastroenterology and Hepatology).

Volume 16 Number 47
December 21, 2010
World J Gastroenterol
2010 December 21; 16(47): 5907-6034

Online Submissions
www.wjgnet.com/1007-9327office
www.wjgnet.com
Printed on Acid-free Paper
世界胃肠病学杂志

A Weekly Journal of Gastroenterology and Hepatology

World Journal of Gastroenterology

A peer-reviewed, online, open-access journal of gastroenterology and hepatology

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2010-2013

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WJG World Journal of Gastroenterology

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Weekly Volume 16 Number 47 December 21, 2010

World Journal of Gastroenterology
Volume 16 Number 47 December 21, 2010

Contents

NAME OF JOURNAL
World Journal of Gastroenterology

LAUNCH DATE
October 1, 1995

RESPONSIBLE INSTITUTION
Department of Science and Technology of Shanxi Province

SPONSOR
Taiyuan Research and Treatment Center for Digestive Diseases, 77 Shuangta Xijie, Taiyuan 030001, Shanxi Province, China

EDITING
Editorial Board of *World Journal of Gastroenterology*,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-5908-0039
Fax: +86-10-8538-1893
E-mail: wjg@wjgnet.com
http://www.wjgnet.com

PUBLISHING
Baishideng Publishing Group Co., Limited,
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai, Hong Kong, China
Fax: +852-3115-8812
Telephone: +852-5804-2046
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

SUBSCRIPTION
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

PRINT SUBSCRIPTION
RMB 245 Yuan for each issue, RMB 11760 Yuan for one year.

ONLINE SUBSCRIPTION
One-Year Price 864.00 USD

PUBLICATION DATE
December 21, 2010

CSSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1007-9327/g_info_20100315215714.htm. If you do not have web access please contact the editorial office.

ONLINE SUBMISSION
http://www.wjgnet.com/1007-9327office

World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i47.5916

World J Gastroenterol 2010 December 21; 16(47): 5916-5924
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

Astrid van der Velde, PhD, *Series Editor*

Scavenger receptor BI: A multi-purpose player in cholesterol and steroid metabolism

Menno Hoekstra, Theo JC Van Berkel, Miranda Van Eck

Menno Hoekstra, Theo JC Van Berkel, Miranda Van Eck, Division of Biopharmaceutics, Leiden/Amsterdam Center for Drug Research, Gorlaeus Laboratories, 2300RA Leiden, The Netherlands

Author contributions: Hoekstra M and Van Eck M contributed equally to the writing of the manuscript; Van Berkel TJC supervised the writing process.

Supported by Top Institute Pharma (TIPharma Project T2-110; Hoekstra M and Van Berkel TJC); Grant 2008T070 from the Netherlands Heart Foundation (Hoekstra M); VIDI Grant 917.66.301 from the Netherlands Organization for Scientific Research (Van Eck M); Van Eck M is an Established Investigator of the Netherlands Heart Foundation (Grant 2007T056)

Correspondence to: Menno Hoekstra, PhD, Division of Biopharmaceutics, Leiden/Amsterdam Center for Drug Research, Gorlaeus Laboratories, Einsteinweg 55, PO Box 9502, 2300RA Leiden, The Netherlands. hoekstra@lacdr.leidenuniv.nl
Telephone: +31-71-5276032 Fax: +31-71-5276032

Received: July 2, 2010 Revised: July 22, 2010
Accepted: July 29, 2010
Published online: December 21, 2010

Abstract

Scavenger receptor class B type I (SR-BI) is an important member of the scavenger receptor family of integral membrane glycoproteins. This review highlights studies in SR-BI knockout mice, which concern the role of SR-BI in cholesterol and steroid metabolism. SR-BI in hepatocytes is the sole molecule involved in selective uptake of cholesteryl esters from high-density lipoprotein (HDL). SR-BI plays a physiological role in binding and uptake of native apolipoprotein B (apoB)-containing lipoproteins by hepatocytes, which identifies SR-BI as a multi-purpose player in lipid uptake from the blood circulation into hepatocytes in mice. In adrenocortical cells, SR-BI mediates the selective uptake of HDL-cholesteryl esters, which is efficiently coupled to the synthesis of glucocorticoids (i.e. corticosterone). SR-BI knockout mice suffer from adrenal glucocorticoid insufficiency, which suggests that functional SR-BI protein is necessary for optimal adrenal steroidogenesis in mice. SR-BI in macrophages plays a dual role in cholesterol metabolism as it is able to take up cholesterol associated with HDL and apoB-containing lipoproteins and can possibly facilitate cholesterol efflux to HDL. Absence of SR-BI is associated with thrombocytopenia and altered thrombosis susceptibility, which suggests a novel role for SR-BI in regulating platelet number and function in mice. Transgenic expression of cholesteryl ester transfer protein in humanized SR-BI knockout mice normalizes hepatic delivery of HDL-cholesteryl esters. However, other pathologies associated with SR-BI deficiency, i.e. increased atherosclerosis susceptibility, adrenal glucocorticoid insufficiency, and impaired platelet function are not normalized, which suggests an important role for SR-BI in cholesterol and steroid metabolism in man. In conclusion, generation of SR-BI knockout mice has significantly contributed to our knowledge of the physiological role of SR-BI. Studies using these mice have identified SR-BI as a multi-purpose player in cholesterol and steroid metabolism because it has distinct roles in reverse cholesterol transport, adrenal steroidogenesis, and platelet function.

Key words: Scavenger receptor class B type I ; High-density lipoprotein; Cholesterol; Lipoprotein metabolism; Liver; Macrophages; Adrenal gland; Platelets; Steroidogenesis

Peer reviewer: Dr. Bart Rik De Geest, Center for Molecular and Vascular Biology, Katholieke Universiteit Leuven, Campus Gasthuisberg, Herestraat 49, Leuven 3000, Belgium

Hoekstra M, Van Berkel TJC, Van Eck M. Scavenger receptor BI: A multi-purpose player in cholesterol and steroid metabolism. *World J Gastroenterol* 2010; 16(47): 5916-5924 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i47/5916.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i47.5916

INTRODUCTION

The scavenger receptor (SR) superfamily consists of integral membrane glycoproteins that are involved in recognition of polyanionic structures of either endogenous [e.g. oxidized low-density lipoprotein (LDL)] or exogenous [e.g. bacterial lipopolysaccharide (LPS)] origin. The SR family is structurally diverse and can be classified into eight different classes (A-H) based on the multi-domain structure of the individual members (reviewed by van Berkel *et al*[1]). The first SR to be cloned was the class A scavenger receptor SR-AI, which was originally identified as a receptor that recognizes acetylated LDL (acLDL). However, due to the limited relevance of acLDL in atherosclerosis, at that time it was primarily considered to be a receptor for negatively charged macromolecules[2]. Macrophage-expressed SR-As can bind many polyanionic molecules such as lipoteichoic acid from Gram-positive bacteria, and lipid IVA, a precursor of lipid A, from LPS of Gram-negative bacteria, as well as mediate uptake of bacteria by phagocytosis. In line with their ability to bind bacteria, class A scavenger receptors play prominent roles in the host response to infection[3,4]. In parallel with SR-As, SR class B type I (SR-BI), also known as CD36 and lysosomal integral membrane protein-Ⅱ analog-1 (CLA-1) in humans, has also been demonstrated to increase the uptake of both Gram-negative and Gram-positive bacteria *in vitro*[5,6].

As its name indicates, SR-BI belongs to the class B subfamily of SRs that also includes its splice variant SR-BII and CD36 (previously known as the OKM5 antigen, platelet glycoprotein Ⅳ, or GP88). The three class B SR proteins show a highly similar structure, which consists of a heavily N-linked glycosylated and fatty acylated protein backbone, which contains a large extracellular loop, two transmembrane domains, and short intracellular N-terminal and C-terminal domains (Figure 1). CD36 and SR-BI represent two distinct proteins that are derived from two different genes located on chromosome 5 in mice and 7 and 12 in humans. SR-BII, however, constitutes an isoform of the *SR-BI* gene, which represents around 40% of total SR-BI/BII mRNA[7]. The SR-BII protein differs from SR-BI only in the C-terminal cytoplasmic tail and contributes to only 12% of the immunodetectable SR-BI/BII protein in mouse liver[7].

Importantly, although SR-BI also modulates susceptibility to sepsis[8,9], it is predominantly known for its functions in lipoprotein metabolism. Since the generation of SR-BI knockout mice that lack a functional SR-BI protein by the group of Monty Krieger in 1997[10], it has become clear that SR-BI is a multi-purpose player in cholesterol and steroid metabolism. In this topic highlight, we review the data obtained from this widely used mouse model regarding the *in vivo* role of SR-BI in cholesterol and steroid metabolism within a wide variety of cells types in mice, including liver parenchymal cells (hepatocytes), adrenocortical cells, macrophages, and platelets. In addition, we discuss recent interesting findings from humanized SR-BI knockout mice that provide the first insight into an important contribution of SR-BI to steroid metabolism and (patho)physiology in humans.

LIVER PARENCHYMAL CELLS

Initial *in vitro* cloning and purification studies performed by the group of Krieger have shown that SR-BI, similar to CD36, displays a high affinity for acLDL, modified proteins (i.e. maleylated bovine serum albumin), and anionic lipids[11,12]. Not long after, it became clear that SR-BI, in addition to its ability to bind (modified) LDL and anionic lipids, can bind high-density lipoprotein (HDL) with a high affinity and saturability[13]. This provided the first evidence that SR-BI could be considered a functional HDL receptor. Immunoblotting on membranes of different murine tissues has revealed that SR-BI protein is highly expressed in liver[13]. The liver is the primary organ that is involved in removal of cholesterol from the body, therefore, much attention has been drawn to a possible role for SR-BI in hepatic lipid transport.

The liver consists of a wide variety of cells including parenchymal cells (hepatocytes), endothelial cells, and Kupffer cells, which represent the largest majority of all tissue macrophages found within the body. Expression profiling has indicated that SR-BI mRNA and protein are particularly high in parenchymal cells, the primary metabolic cell type of the liver[14,15]. However, SR-BI is also detected in Kupffer cells, albeit at a lower expression level[14,16]. In accordance with a role for SR-BI in hepatocyte HDL-cholesterol clearance, liver parenchymal cells are responsible for 88% of the hepatic uptake of cholesteryl esters from HDL in wild-type mice, when taking into account the contribution of these cells to liver mass[17]. Importantly, we have been able to show that SR-BI is responsible for the majority of the uptake of HDL-cholesteryl esters into the liver. Functional SR-BI deficiency in SR-BI knockout mice was associated with an 87% and 52% decrease in uptake of HDL-cholesteryl esters in liver parenchymal and Kupffer cells, respectively, compared with wild-type littermate controls[17]. *In vitro* association studies showed uptake of HDL-cholesteryl esters without whole particle internalization (selective uptake) in isolated liver parenchymal cells of wild-type mice, which was completely lost in those of SR-BI knockout mice. This suggests that, at least in mice, SR-BI is the sole molecule that is involved in the selective uptake of HDL-associated cholesteryl esters in hepatocytes[17]. In parallel with the major role of the liver in the clearance of HDL-associated cholesterol from the blood circulation, SR-BI knockout mice exhibit a marked increase in their plasma HDL-cholesterol levels. Already on a regular chow diet, in these mice an accumulation of larger, but not more, cholesteryl-ester-rich HDL particles can be observed[10], probably as a result of the diminished selective uptake of HDL-cholesteryl esters by SR-BI in the liver. In addition, SR-BI attenuated mice, with an SR-BI promoter mutation that resulted in 53% decreased expression of the receptor in the liver, displayed a lower hepatic selective HDL-cho-

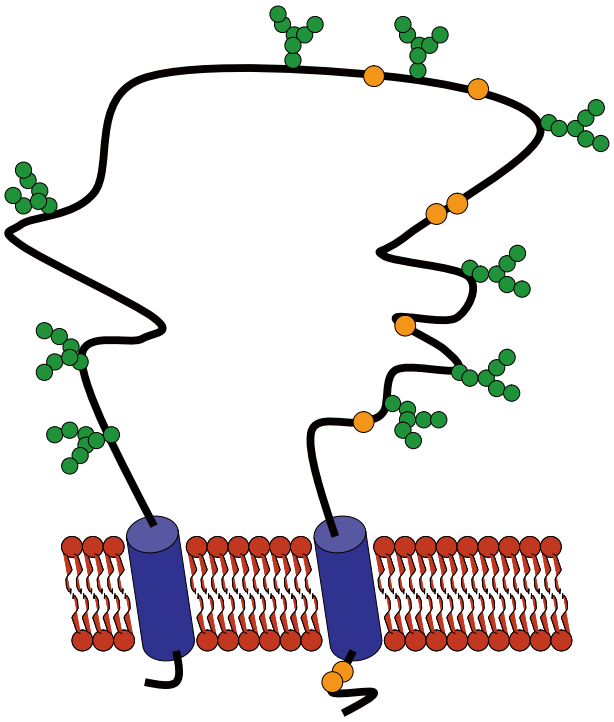

Figure 1 Schematic representation of the scavenger receptor class B type I protein. Structural elements include a heavily N-glycosylated and fatty-acylated protein backbone that contains a large extracellular loop, two transmembrane domains, and short intracellular N-terminal and C-terminal domains.

lesteryl ester uptake and a higher plasma HDL-cholesterol level[18]. Furthermore, transgenic or adenoviral overexpression of SR-BI in hepatocytes is associated with virtual disappearance of HDL from the plasma compartment[19-22]. These findings convincingly show that SR-BI in mice is a functional HDL receptor in liver parenchymal cells.

SR-BI knockout mice also display a significant increase in the level of cholesterol associated with the plasma non-HDL fraction[10,23,24]. In parallel, transgenic mice that have liver-specific overexpression of SR-BI show a decrease in LDL- and very low density lipoprotein (VLDL)-cholesterol levels[20]. These observations suggest that SR-BI can also contribute to the clearance of apoB-containing lipoproteins *in vivo*. To verify this hypothesis, several groups have studied uptake of apoB100-containing LDL and VLDL lipoproteins, as well as apoB48-containing chylomicrons in hepatocytes from SR-BI knockout mice and their wild-type littermate controls. Rhainds *et al*[25] and Bourret *et al*[26] have detected a dose-dependent decrease in the selective uptake of cholesteryl esters associated with human LDL by liver parenchymal cells isolated from heterozygous (-45%) and homozygous (-87%) SR-BI knockout mice[25,26]. In parallel, the uptake of triglyceride-rich, chylomicron- remnant-like emulsion particles by liver parenchymal cells of homozygous SR-BI knockout mice is markedly lower compared to that of wild-type controls[27]. Furthermore, the association with and apparent uptake of β-VLDL is 1.6-2.2-fold decreased in hepatocytes isolated from SR-BI knockout mice *in vitro*[24], whereas the serum decay and hepatic uptake of β-VLDL is significantly diminished in response to SR-BI deficiency *in vivo*[24]. Moreover, SR-BI knockout mice show a higher postprandial triglyceride response to an intragastric fat load[27]. SR-BI deficiency, however, does not alter the ability of oxidized LDL to associate with liver parenchymal cells *in vitro*[26]. It thus seems that SR-BI also plays a physiological role in the binding and uptake of native, but not modified, apoB-containing lipoproteins by liver parenchymal cells *in vivo*. Combined with the fact that SR-BI is a functional HDL receptor *in vivo*, SR-BI can be considered a multi-purpose player in lipid uptake from the blood circulation into hepatocytes in mice.

ADRENOCORTICAL CELLS

Although SR-BI plays a widely recognized role in hepatic clearance of lipids, the highest protein expression of SR-BI is actually found in the adrenal glands[13]. More specifically, adrenocortical cells (i.e. Y1-BS1 murine adrenal cells) contain relatively high levels of SR-BI protein that are predominantly localized in cholesterol-rich caveolin-1-containing domains within the plasma membrane[28]. Cells within the adrenal cortex are involved in the synthesis of cholesterol-derived steroid hormones, including mineralocorticoids (i.e. aldosterone) and glucocorticoids (i.e. cortisol in humans and corticosterone in rodents). In the original 1997 study on the effect of the targeted mutation in the SR-BI gene on cholesterol metabolism *in vivo*, it was described that the adrenal cholesterol content was dose-dependently decreased in heterozygous (-42%) and homozygous (-72%) SR-BI knockout mice[10]. In accordance, the uptake of cholesteryl esters from HDL by the adrenals of SR-BI knockout mice is reduced[17]. Strikingly, however, in 2008, we and others were able to show that the impaired uptake of HDL-cholesteryl esters by the adrenal glands translates into functional changes in the adrenal steroidogenesis rate in SR-BI knockout mice. Adrenal SR-BI deficiency is associated with increased adrenal weight as a result of long-term overstimulation of adrenocortical cell proliferation by the pituitary-derived adrenocorticotropic hormone (ACTH)[10,29]. Under basal non-stressed conditions, plasma glucocorticoid levels (i.e. corticosterone) in SR-BI knockout mice are maintained within the normal range, probably as a result of the high level of circulating ACTH, a potent activator of adrenal steroidogenesis[8,29]. In contrast, SR-BI knockout mice are unable to increase plasma corticosterone levels upon a variety of stress triggers that activate the hypothalamus-pituitary-adrenal axis, which results in increased secretion of glucocorticoids by adrenocortical cells in the zona fasciculata. We have shown that the fasting-induced adrenal glucocorticoid response is significantly diminished in SR-BI knockout mice, resulting in a approximately 50% lower fasting plasma glucocorticoid level[29,30]. The adrenal cortex is virtually depleted of neutral lipids (i.e. cholesteryl esters) in SR-BI knockout mice under fasting stress conditions, which is associated with a visual change in the appearance of the adrenal glands (red/brownish color instead of

white)[10,29]. In parallel with fasting-induced glucocorticoid insufficiency, adrenals of SR-BI knockout mice are also unable to respond to a potent inflammatory stress trigger. Upon LPS exposure, wild-type mice show a significant increase in their plasma corticosterone levels. Plasma corticosterone levels, however, are not induced in SR-BI knockout mice challenged with LPS[8,30]. Glucocorticoids are important signaling molecules that through the action of their cognate nuclear receptor mediate downstream effects on energy homeostasis and the control of immune responses. In accordance, SR-BI knockout mice exhibit fasting hypoglycemia, which is paralleled by reduced expression of hepatic glucocorticoid targets involved in fatty acid utilization[29]. Furthermore, the LPS-induced cytokine (i.e. tumor necrosis factor-α and interleukin-6) response is enhanced, probably due to an impaired suppressive action of glucocorticoids on pro-inflammatory gene expression in macrophages and other immune cells, which leads to an overall higher LPS-induced mortality rate in SR-BI knockout mice[8]. In line with a prominent role for SR-BI in the generation of the substrate used for adrenal steroidogenesis under stress conditions, SR-BI expression in adrenocortical cells is tightly controlled by the steroidogenic activator ACTH *in vitro* and *in vivo*[31,32]. These findings suggest that functional SR-BI protein is necessary for optimal adrenal steroidogenesis in mice.

MACROPHAGES

Macrophages cannot limit the uptake of excess cholesterol and thus rely on active cholesterol efflux processes to maintain their intracellular cholesterol balance. As a result, disruption of the function of proteins crucially involved in macrophage cholesterol efflux is associated with the formation of so-called foam cells, which are large lipid-filled macrophages. The cholesterol transport protein ATP-binding cassette transporter A1 (ABCA1) has been shown to be a major player in macrophage cholesterol efflux. Ablation of ABCA1 function is associated with almost complete shutdown of cholesterol efflux from macrophages to apolipoprotein AI (apoAI), and enhanced foam cell formation *in vitro* and *in vivo*[33-35]. Lipidation of apoAI is the primary step in the formation of HDL, which executes the transport of cholesterol from peripheral cells (i.e. macrophages) back to the liver for subsequent excretion into the bile, a process also known as reverse cholesterol transport (reviewed by Van Eck *et al*[36]). SR-BI is a major player in the final step of reverse cholesterol transport because it, as discussed previously, mediates the selective uptake of HDL-cholesteryl esters into the liver.

Initial overexpression studies by Ji *et al*[37] have shown a clear correlation between the level of cellular cholesterol efflux to mature HDL and the expression levels of SR-BI protein *in vitro*, which suggests that SR-BI also mediates the primary step in reverse cholesterol transport *in vivo*. Follow-up studies have indicated that SR-BI does indeed mediate cholesterol efflux to HDL in cells that have been labeled with unesterified cholesterol[38]. Strikingly, however, SR-BI has been shown not to influence the efflux of cholesterol from macrophages that are loaded with cholesterol packaged in acLDL[38]. Furthermore, it actually decreases the efflux of cholesterol to apoAI *via* ABCA1 in RAW macrophages, which could be attributed the ability of SR-BI to re-uptake cholesterol after ABCA1-mediated efflux[38]. These studies were the first to show that SR-BI and ABCA1 have distinct and competing roles in mediating cholesterol flux between (pre-β) HDL and macrophages. In line with a role for SR-BI in cholesterol uptake, the association of β-VLDL and HDL in peritoneal macrophages is reduced in response to SR-BI deficiency[39]. Studies *in vitro*, however, have either shown that SR-BI does modulate cholesterol efflux[37] or have argued against a role for SR-BI in efflux in general[40-42]. To date, the quantitative role for SR-BI in macrophage cholesterol efflux has therefore been under discussion and this has contributed to the mystification of SR-BI as a player in cholesterol efflux from macrophages.

Thioglycolate-elicited peritoneal macrophages from SR-BI knockout mice loaded with unesterified cholesterol *in vivo* and subsequently subjected to cholesterol efflux *in vitro* displayed a 20% reduced efflux to mature HDL as compared to wild-type macrophages[39]. To study the quantitative role of different transport proteins in cholesterol efflux in mice, the group of Dan Rader has developed an experimental *in vivo* reverse cholesterol transport model. *In vitro* cholesterol-labeled bone marrow-derived or peritoneal macrophages from specific knockout mice are injected into recipient mice and subsequently the appearance of cholesterol in the plasma compartment, uptake by the liver, and the rate of sterol excretion into the feces are monitored. Using this experimental model, no effect of macrophage SR-BI deficiency on macrophage cholesterol efflux/reverse cholesterol transport was detected, because the cholesterol distribution in plasma as well as fecal tracer levels were no different upon injection of peritoneal or bone-marrow-derived macrophages from SR-BI knockout mice and their wild-type littermates into C57BL/6 recipient mice[43]. However, macrophages were cultured *in vitro* for at least 24 h before injection into recipient mice. *In-vitro*-cultured macrophages might display an altered expression of cholesterol transport proteins as compared to macrophages *in vivo*. In this respect, the absence of an effect of macrophage SR-BI deficiency in the described reverse cholesterol transport model might not necessarily imply that SR-BI does not affect the cholesterol efflux potential of macrophages *in vivo*.

In our opinion, too little knowledge is currently present about which type of macrophage and cholesterol acceptor combination *in vitro* best represents the *in vivo* situation. We anticipate that large-scale genomic and proteomic analysis on freshly isolated (tissue) macrophage foam cells, as well as peritoneal and bone-marrow-derived macrophages cultured under different loading conditions (i.e. unesterified cholesterol, acLDL, oxidized LDL) is needed to provide clues as to which setting might actually

be useful to study functional consequence of specified gene targets on cholesterol efflux *in vivo*. Although we appreciate an important role for SR-BI in cholesterol efflux, we encourage novel research into this interesting topic, which will unravel not only the contribution of SR-BI, but also clarify the interaction between the different cholesterol efflux pathways.

PLATELETS

Early evidence in several disease states in humans (e.g. familial hyperlipidemia) has suggested an interaction between cholesterol-containing lipoproteins and platelets[44,45]. As a consequence, the modulation of platelet functions by lipoproteins has been investigated intensively both in humans and animal models. Due to the large fluctuation in their plasma concentrations, the data on the influence of triglyceride-rich lipoproteins, such as chylomicrons and VLDL, are limited. In contrast, numerous studies have demonstrated a distinctive interaction of platelets with LDL and HDL (reviewed by Korporaal *et al*[46]).

Platelets are able bind to rapidly and reversibly to HDL in an activation-state- and temperature-independent manner with a Kd of 11-60 nmol/L[47,48]. The number of HDL binding sites expressed on the platelet surface ranges from 1200 to 3200 copies[47,48]. Koller *et al*[48,49] have observed that LDL interferes with the binding of HDL to platelets as a result of overlapping affinities for different receptors. In 1986, the same group described CD41 and CD61, the two constituents of integrin αⅡbβ3, as binding proteins for HDL on the platelet surface. An antibody directed against the integrin β3-subunit blocked the binding of HDL to integrin αⅡbβ3 on the platelet surface, thereby identifying αⅡbβ3 as the platelet receptor for HDL[49]. In contrast with these observations, others have reported that αⅡbβ3 is not involved in binding of HDL to platelets, because: (1) antibodies directed against integrin αⅡbβ3 have no effect; (2) HDL does not alter agonist-induced fibrinogen binding or platelet aggregation[50,51]; (3) HDL-induced platelet signaling is similar in control platelets and platelets from thrombasthenic patients with abnormal levels of αⅡbβ3 and fibrinogen[52]; (4) treatment of platelets with EDTA, which causes dissociation of the integrin complex and fully inhibits fibrinogen binding and platelet aggregation[53], does not inhibit the interaction between HDL and platelets[54]; and (5) αⅡbβ3 ligands like fibrinogen, fibronectin, vitronectin, and von Willebrand factor do not affect HDL binding[52]. It therefore remains unclear which receptor is the actual binding site for HDL in platelets.

In 2003, Imachi *et al*[55] identified SR-BI as being expressed on human platelets, which opened up the possibility that, as in the liver, adrenals, and macrophages, SR-BI acts as a functional HDL receptor in platelets. *In vitro* association studies by Valiyaveettil *et al*[56] have proved that oxidized HDL (oxHDL) binds to isolated platelets in an SR-BI-dependent manner. Binding of oxHDL could be diminished by pre-incubation of platelets with an SR-BI blocking antibody, whereas native HDL decreased oxHDL binding to human platelets[56]. In parallel, the oxHDL-induced repression of platelet aggregation *in vitro* was almost fully blocked by inhibiting SR-BI binding, which suggests that a direct interaction of HDL with SR-BI is necessary to alter normal platelet function[56]. To validate the functional role of SR-BI in platelets *in vivo*, the group of Monty Krieger has evaluated platelet function in SR-BI knockout mice and their littermate controls. SR-BI knockout mice suffer from thrombocytopenia, because their blood platelet counts are markedly reduced as a result of enhanced clearance of platelets by the reticuloendothelial system[57]. Probably as a compensatory response, splenic megakaryocyte (platelet precursor) counts are increased in SR-BI knockout mice[57]. Elegant crossover platelet infusion studies have shown that the increased turnover of platelets is not primarily due to genotype-induced changes in the platelets themselves, but rather is secondary to the high level of HDL-associated unesterified cholesterol that circulates in the plasma of SR-BI knockout mice. As unesterified cholesterol rapidly exchanges between the plasma compartment and blood cells, including platelets, SR-BI knockout platelets contain relative high cellular levels of cholesterol, which is associated with a functional impairment of the aggregation in response to ADP[57]. In parallel, we have shown that SR-BI deficiency and the dyslipidemia associated with it lead to thrombocytopenia and impaired platelet reactivity *ex vivo* as a result of the increased platelet cholesterol content[58]. In addition, SR-BI deficiency in mice is associated with enhanced thrombosis susceptibility[58]. However, platelet-specific deficiency of SR-BI is associated with resistance to hyper-reactivity induced by increased platelet cholesterol content[59], which suggests that SR-BI contributes to platelet function *in vivo*. In accordance, platelet-specific SR-BI modulates thrombosis susceptibility in SR-BI knockout mice[59]. These findings highlight an interesting novel role for SR-BI in regulating platelet number and function and thrombosis susceptibility in mice.

POTENTIAL FOR SR-BI IN CHOLESTEROL AND STEROID METABOLISM IN HUMANS: INSIGHTS FROM HUMANIZED SR-BI KNOCKOUT MICE

From the combined findings in SR-BI knockout mice it can be concluded that SR-BI is a multi-purpose player in cholesterol and steroid metabolism in mice. Several clinical studies have detected significant associations between several polymorphisms at the SR-BI locus and changes in plasma lipid levels and lipoprotein particle sizes[60-62]. Human subjects, in contrast to rodents, express cholesteryl ester transfer protein (CETP) that is able to transfer cholesteryl esters from HDL to the apoB-containing lipoproteins VLDL and LDL, in exchange for triglycerides. As a result, human subjects carry most of their cholesterol in the LDL fraction, whereas mice predominantly transport

their plasma lipids in HDL. The CETP→LDL→LDL receptor route provides an alternative for HDL-cholesteryl ester delivery from the blood circulation to the liver, which might be associated with a relatively limited uptake of HDL-cholesteryl esters *via* SR-BI into the liver in humans compared with mice. To date, no functional mutations in the *SR-BI* gene have been identified, therefore, the relative contribution of SR-BI to lipoprotein metabolism in humans is therefore still unclear.

To gain insight in the importance of SR-BI in the human situation, studies have been performed in humanized SR-BI knockout mice that express the *CETP* gene under the control of its natural regulatory elements. In these SR-BI knockout/CETP transgenic mice, similar to the human situation, relatively high mRNA expression levels of CETP can be detected in adipose tissue and macrophage-rich tissues such as the liver and spleen[30]. In accordance with the assumption that the CETP→LDL →LDL receptor route can provide an alternative for the delivery of HDL-associated cholesteryl esters to the liver in humans, transgenic expression of CETP is able to normalize almost fully the serum decay and hepatic uptake of HDL-cholesteryl esters in SR-BI knockout mice[63,64]. As a result, plasma total cholesterol levels are significantly lower in SR-BI knockout/CETP transgenic mice as compared to SR-BI knockout mice[30,63,64]. Importantly, plasma lipid levels as well as lipoprotein particle sizes are not fully restored. Plasma unesterified cholesterol levels, the unesterified cholesterol to total cholesterol ratio, and HDL particle size are only mildly decreased by CETP expression[63]. In parallel with previous findings of Dole *et al*[57], the increased unesterified cholesterol levels in SR-BI knockout mice with or without CETP expression are associated with a lower platelet count and reduced platelet aggregation[63]. CETP expression increases, but does not normalize, adrenal uptake of HDL-associated cholesteryl esters in SR-BI knockout mice. Strikingly, the stress-induced adrenal glucocorticoid insufficiency, however, is equally severe in SR-BI knockout mice with or without CETP expression[30]. Furthermore, the higher tissue oxidative status previously detected in SR-BI knockout mice[65] does not return to basal levels in mice that express the CETP transgene[63]. Changes in plasma lipid levels (i.e. an increase in apoB-containing lipoproteins or a decrease in HDL)[66], an increased adrenal steroidogenesis rate[67] as well as modified platelet function[68] underlie the process of atherothrombosis, the primary cause of cardiovascular disease mortality and morbidity. SR-BI deficiency in mice is associated with enhanced susceptibility to atherosclerotic lesion development[23]. This finding indicates that high HDL-cholesterol levels *per se* do not protect against atherosclerosis and underlines that other parameters regarding HDL function should be established and evaluated in the clinical setting. Expression of CETP also does not provide protection against atherosclerosis in SR-BI knockout mice[63]. Overall, it thus seems that, although CETP activity can restore the transport of HDL-cholesteryl esters to the liver in SR-BI knockout mice, it cannot normalize many other processes associated with disruption of the *SR-BI* gene in mice.

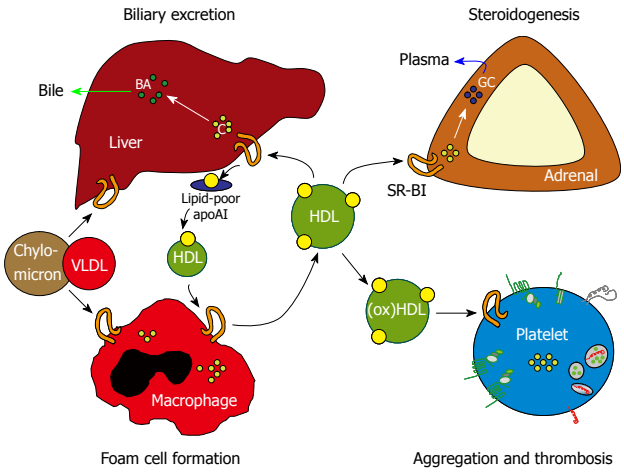

Figure 2 Overview of the diverse role of scavenger receptor class B type I in cholesterol and steroid metabolism in mice. (1) In liver, scavenger receptor class B type I (SR-BI) mediates the selective uptake of cholesterol (C; yellow) from high-density lipoprotein (HDL) that is subsequently converted to bile acids (BA; green) for biliary excretion; (2) HDL-associated cholesteryl esters are taken up *via* SR-BI in adrenocortical cells, which is efficiently coupled to the synthesis and subsequent secretion of glucocorticoids (GC; blue) into plasma; (3) SR-BI binds apolipoprotein (apo)B-containing lipoproteins, i.e. chylomicrons and very low density lipoprotein (VLDL), in liver and macrophages, which contributes to macrophage foam cell formation; (4) SR-BI is able to efflux cholesterol from macrophages to small HDL particles, which inhibits foam cell formation; and (5) HDL can interact with platelets, in part *via* the direct action of SR-BI, to modulate platelet aggregation and susceptibility to thrombosis.

CONCLUSION

The initial generation of the SR-BI knockout mice by the group of Monty Krieger has significantly contributed to our knowledge of the physiological role of SR-BI. Studies using these mice have identified SR-BI as a multi-purpose player in cholesterol and steroid metabolism, because it has distinct roles in reverse cholesterol transport, adrenal steroidogenesis, and platelet function (summarized in Figure 2). Recent studies have suggested a potential role for HDL and SR-BI in the control of endothelial cell[69-71] and stem and progenitor cell[72,73] physiology, and we are confident that upcoming research using SR-BI knockout mice will also reveal the importance of SR-BI in these additional cell systems.

Based upon the findings from humanized CETP transgenic SR-BI knockout mice, we anticipate that functional SR-BI mutations in humans who do naturally express CETP will be associated with various diseases (i.e. adrenal glucocorticoid insufficiency, impaired platelet function, and enhanced atherogenesis) similar to those observed in SR-BI knockout mice. We hope that functional mutations in the *SR-BI* gene will be identified in the near future as a result of large-scale DNA screening studies in human subjects that have relatively high plasma HDL-cholesterol levels. If changes in SR-BI function in humans are indeed associated with an increased susceptibility for atherosclerotic

rosis, this will further establish the importance of SR-BI as a therapeutic target for increasing HDL-mediated reverse cholesterol and lowering clinical atherosclerosis and the associated cardiovascular disease risk.

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