Atherosclerosis xxx (2017) 1–9

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

SR-BI as target in atherosclerosis and cardiovascular disease - A comprehensive appraisal of the cellular functions of SR-BI in physiology and disease

Menno Hoekstra

Division of Biopharmaceutics, Cluster BioTherapeutics, Leiden Academic Centre for Drug Research (LACDR), Gorlaeus Laboratories, Einsteinweg 55, 2333CC Leiden, The Netherlands

ARTICLE INFO

Article history:
Received 13 December 2016
Received in revised form
25 January 2017
Accepted 27 January 2017
Available online xxx

Keywords:
SR-BI
High-density lipoprotein
Atherosclerosis
Cell types
Cardiovascular disease
Knockout mice

ABSTRACT

High-density lipoprotein (HDL) is considered an anti-atherogenic lipoprotein species due to its role in reverse cholesterol transport. HDL delivers cholesterol esters to the liver through selective uptake by scavenger receptor class B type I (SR-BI). In line with the protective role for HDL in the context of cardiovascular disease, studies in mice and recently also in humans have shown that a disruption of normal SR-BI function predisposes subjects to the development of atherosclerotic lesions and cardiovascular disease. Although SR-BI function has been studied primarily in the liver, it should be acknowledged that the SR-BI protein is expressed in multiple tissues and cell types across the body, albeit at varying levels between the different tissues. Given that SR-BI is widely expressed throughout the body, multiple cell types and tissues can theoretically contribute to the atheroprotective effect of SR-BI. In this review the different functions of SR-BI in normal physiology are highlighted and the (potential) consequences of cell type-specific disruption of SR-BI function for atherosclerosis and cardiovascular disease susceptibility discussed. It appears that hepatocyte and platelet SR-BI inhibit respectively the development of atherosclerotic lesions and thrombosis, suggesting that SR-BI located on these cell compartments should be regarded as being a protective factor in the context of cardiovascular disease. The relative contribution of SR-BI present on endothelial cells, steroidogenic cells, adipocytes and macrophages to the pathogenesis of atherosclerosis and cardiovascular disease remains less clear, although proper SR-BI function in these cells does appear to influence multiple processes that impact on cardiovascular disease susceptibility.

1. Scavenger receptor BI (SR-BI): a therapeutic target in the context of cardiovascular disease

Relatively high plasma low-density lipoprotein (LDL)-cholesterol levels are a major risk factor for the development of cardiovascular disease [1]. As such, treatment with statins that inhibit cholesterol synthesis leading to a compensatory increase in hepatic LDL receptor expression and LDL whole particles uptake by the liver, constitutes the primary cardiovascular therapy. New LDL-cholesterol lowering approaches have recently also been validated, e.g. inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) activity [2,3], that impact by other means on LDL receptor protein expression and functionality. A 21% reduction in any major vascular event and only a 12% reduction in mortality from any vascular cause is achieved per 1 mmol/L decrease in LDL-cholesterol levels [4]. A considerable residual risk to develop cardiovascular disease thus remains, which highlights the need for additional therapeutic approaches to treat patients at risk of cardiovascular disease that are not solely based upon lowering of LDL-cholesterol levels.

Apolipoprotein A1 (apoA1)-containing high-density lipoprotein (HDL) is considered an anti-atherogenic lipoprotein species as (1) HDL particles can accept cholesterol from foam cells to reduce intracellular cholesterol ester stores [5] and (2) low plasma HDL-cholesterol levels are associated with an increased risk for cardiovascular disease [1]. HDL removes excess cholesterol from the body via reverse cholesterol transport for biliary excretion through an interaction with the HDL receptor scavenger receptor class B type I (SR-BI) present on the liver [6]. Interestingly, in line with the

E-mail address: Hoekstra@lacdr.leidenuniv.nl.

http://dx.doi.org/10.1016/j.atherosclerosis.2017.01.034

protective role for HDL in the context of cardiovascular disease, studies in mice and recently also in humans have shown that disruption of the normal HDL/SR-BI interaction is associated not only with an accumulation of HDL-cholesterol in the plasma compartment but also an increased risk for the development of atherosclerotic lesions and cardiovascular disease. More specifically, human carriers of functional mutations in the *SCARBI* gene, that codes for the SR-BI protein, generally exhibit very high HDL-cholesterol levels, i.e. ≥95th percentile of values for the general population [7–9]. In addition, SR-BI knockout mice as compared to wild-type littermate controls also exhibit a marked increase in plasma HDL-cholesterol levels [10]. Total body SR-BI deficiency increases the risk for atherosclerosis 72-fold in wild-type mice when challenged with a Western-type diet enriched in cholesterol and fat [10], whilst the P376L loss-of-function mutation in the human SR-BI gene is associated with a 1.79-fold increased risk for the development of coronary artery disease [7]. SR-BI can therefore be regarded a putative novel cardiovascular therapeutic target.

2. SR-BI: a unique player in lipoprotein metabolism

Since the original discovery by the group of Monty Krieger, in 1996, that HDL is a functional HDL receptor [11], much has been learned about the transcriptional control, structure and function of the protein. SR-BI and its splicing isoform SR-BII [12] belong to the scavenger receptor superfamily of membrane proteins that recognize a broad array of ligands (reviewed by Van Berkel et al. [13]). SR-BI and SR-BII consist of small N- and C-terminal cytoplasmic domains, two transmembrane domains, and a large extracellular loop containing multiple sites for N-linked glycosylation. The proteins are expressed in multiple tissues and cell types across the body, albeit at varying levels between the different isoforms and tissues [10,12].

As reviewed by Leiva et al. cellular expression of SR-BI is regulated both at the transcriptional and post-transcriptional level [15]. Nuclear receptors as well as intracellular signaling pathways directly modulate the rate of SR-BI gene transcription, whilst estrogen impacts on SR-BI transcript levels through its effect on SR-BI/SR-BII splicing. Of note, SR-BI mRNA expression is upregulated in response to cellular cholesterol depletion [16], suggesting that increasing HDL-associated cholesterol uptake by SR-BI could be a general back-up mechanism for cholesterol delivery to cells under conditions of hypocholesterolemia. For its membrane localization in the liver SR-BI is highly dependent on an interaction with a scaffolding protein called PDZ domain containing 1 (PDZK1) that interacts with the C-terminus of SR-BI [17,18]. Studies in which the C-terminus of SR-BI was selectively depleted in mice have indicated that a similar mechanism may be in place to facilitate membrane expression of SR-BI in adrenocortical cells [19]. Recent studies by Pollard et al. have suggested that specific localization of SR-BI on the plasma membrane may also be controlled by procollagen C-endopeptidase enhancer protein 2 (PCPE2) [20].

In line with its scavenging function, SR-BI is able to bind a wide variety of ligands including anionic phospholipids, native and modified LDL particles, HDL species, and apoptotic cells [21–23]. Studies by Pagler et al. have shown that SR-BI can transfer cholesterol from lipoproteins to cells through whole particle uptake/endocytosis [24]. However, SR-BI is primarily known for its unique role in the selective uptake of cholesterol esters from lipoproteins without parallel uptake of the whole particle. As depicted in Fig. 1, the selective uptake process consists of three steps: 1) binding of cholesterol ester-rich lipoprotein particles to the loop domain of SR-BI and 2) the transfer of cholesterol esters to the plasma membrane, and 3) the release from the cholesterol-poor lipoprotein particles back into the blood circulation [25,26]. Although with the discovery of SR-BI it became more evident that cholesterol esters can be selectively taken up from HDL particles, it is important to acknowledge that the concept of selective lipid uptake had already been established through pioneering work of Dr. Pittman and coworkers far before the discovery of SR-BI [27,28]. It is generally believed that initial particle binding and subsequent selective transfer of cholesterol esters are independent from each other. However, much needs to be learned regarding the exact mechanism of action behind SR-BI-mediated selective cholesterol uptake. Piloting findings from mutagenesis studies have suggested that subdomains in the N-terminal and C-terminal regions of the extracellular domain of SR-BI, and in particular tryptophan 415, are of critical importance for both lipoprotein binding and selective HDL-cholesterol ester uptake by SR-BI [29,30].

Given that SR-BI is widely expressed throughout the body, multiple cell types and tissues can theoretically contribute to the atheroprotective effect of SR-BI. The aim of this review is to highlight the different functions of SR-BI in normal physiology and discuss the (potential) consequences of cell type-specific disruption of SR-BI function for atherosclerosis and cardiovascular disease susceptibility.

3. SR-BI in hepatocytes

SR-BI-mediated uptake of HDL-cholesterol esters into the liver is regarded as the final step in the anti-atherogenic reverse cholesterol transport process [6,31]. As such, much attention has been drawn on determining the hepatic sub-cellular localization of SR-BI. Ganesan et al. have recently published a controversial imaging study which suggests that SR-BI is primarily localized to sinusoidal endothelial cells within the liver [32]. Although SR-BI is present in liver endothelial cells, several lines of evidence challenge the notion of Ganesan et al. that SR-BI is not expressed in hepatocytes. Rescue of endothelial cell SR-BI function in total body SR-BI knockout mice does not the reverse the hypercholesterolemia, i.e. accumulation of free cholesterol-enriched HDL particles associated with global murine SR-BI deficiency [33]. In addition, biochemical assays on well-characterized isolated liver cell populations have indicated that the great majority of SR-BI mRNA and protein expression within the liver is actually localized to hepatocytes [34,35]. More importantly, genetic deletion of SR-BI function fully eliminates the ability of hepatocytes to selectively take up cholesterol esters from HDL both in vitro and in vivo [36,37], providing also functional proof for an important physiological role of hepatocyte SR-BI in HDL metabolism. A similar impairment in the selective uptake of cholesterol esters from HDL has been observed in cultured hepatocytes pre-incubated with SR-BI/SR-BII antiserum [38].

The sole contribution of hepatocytes to SR-BI's atheroprotective effect has not been specifically addressed in normolipidemic wild-type mice. However, studies by Huby et al. have shown that an additional deletion of hepatocyte SR-BI function in hypomorphic SR-BI knockout mice, that exhibit a reduced expression of SR-BI in multiple non-hepatic tissues, is necessary to dramatically increase the susceptibility for the development of atherosclerotic lesions [39]. In support of an anti-atherogenic function of hepatocyte SR-BI, liver-specific adenoviral overexpression of SR-BI in hyperlipidemic LDL receptor knockout mice has been shown to lower atherosclerosis susceptibility [40]. Furthermore, liver-specific SR-BI deficiency in PDZK1 knockout mice increases atherosclerosis susceptibility in hyperlipidemic apolipoprotein E (apoE) knockout mice [41]. Moreover, liver-directed transgenic overexpression of SR-BI decreases the atherosclerosis extent in heterozygous LDL receptor knockout mice fed a cholic acid-containing atherogenic diet [42]. The latter studies by Arai et al. have suggested that at least a part of the protection against atherosclerosis associated with SR-BI

Please cite this article in press as: M. Hoekstra, SR-BI as target in atherosclerosis and cardiovascular disease - A comprehensive appraisal of the cellular functions of SR-BI in physiology and disease, Atherosclerosis (2017), http://dx.doi.org/10.1016/j.atherosclerosis.2017.01.034