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Antiatherogenic role of high-density lipoproteins: insights from genetically engineered-mice

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1. ABSTRACT

Plasma levels of high-density lipoprotein (HDL) cholesterol are inversely correlated with the incidence of atherosclerotic cardiovascular disease. The cardioprotective effects of HDL have been attributed to its role in reverse cholesterol transport (RCT) and especially the macrophage-dependent RCT, and also to the antioxidant properties of HDL as well as its direct effects on endothelial function. However, few of these effects have been verified *in vivo* in humans. With the creation and detailed analysis of genetically-engineered mice, a solid body of new information has emerged on the mechanisms controlling these key antiatherogenic functions of HDL and their effects on atherogenesis. This article provides a review of new insights into the molecular mechanisms underlying these three most studied antiatherogenic functions of HDL *in vivo* with a focus on genetically-engineered mice.

2. INTRODUCTION

High-density lipoproteins (HDL) constitute one of the quantitatively predominant lipoprotein families present in plasma which contain approximately equal amounts of lipid and protein. This lipoprotein family is very heterogeneous in particle size (Stocke's diameter from 5 to 17 nm), apolipoprotein (apo) composition and density (which varies between 1.063 g/ml and 1.21 g/ml). HDL particles are classified, according to the content of their major apolipoproteins (apos), into those containing apoA-I (LpA-I) and those containing both apoA-I and apoA-II (LpA-I/A-II) (1). These predominant HDL fractions migrate in agarose gels with α-electrophoretic mobility. Approximately 5 to 15% of apoA-I in plasma is associated with particles with preβ- electrophoretic mobility. The origin of this particle is not clear. Several mechanisms have been proposed, including direct secretion into plasma from

hepatocytes or enterocytes, release during interconversion of α-HDL subpopulations by phospholipid transfer protein (PLTP), cholesteryl ester transfer protein (CETP), hepatic lipase (HL), endothelial lipase (EL), or direct interaction of free apolipoproteins with cell membrane (2).

Clinical and epidemiological studies have demonstrated an inverse correlation between the concentration of plasma HDL cholesterol (HDLc) and the incidence of atherosclerotic cardiovascular disease (3, 4), suggesting that HDL protects against atherosclerosis. The importance of HDL is underscored by the increased incidence of atherosclerosis in patients with familial hypoalphalipoproteinemia (5, 6). Further, the antiatherogenic capacity of HDL has been well documented in several studies in transgenic mice and rabbits (7-12). Nevertheless, the relationship between HDL and atherosclerosis is complex and has exceptions. For example, patients with very infrequent genetic alterations which cause almost total deficiency of HDL do not appear to have a greater risk of suffering cardiovascular disease than control subjects (2, 13). This feature has recently been reproduced in animals in which genes of vital HDL proteins have been specifically knocked out (14, 15). As an explanation for these discrepancies, it had been postulated that the relationship between the concentration of HDLc and cardiovascular disease might only be secondary to alterations in the metabolism of lipoproteins rich in triglycerides (2).

Many quantitative trait loci (QTL) have been found which regulate plasma levels for HDLc. Most of these human QTL have concordant mouse QTL mapping to homologous regions, suggesting that many mouse genes involved in HDL metabolism may also regulate the same traits in humans (16). However, the significance of these proteins involved in HDL metabolism is controversial, especially those which would be determinant in their antiatherogenic action. HDL may mediate atheroprotection via multiple mechanisms, which include reverse cholesterol transport (RCT), prevention of LDL oxidative modification and modulation of endothelial signaling events. This topic has been the focus of several recent excellent reviews (17-20). This complexity emphasizes that changes in HDL function rather than changes in HDLc determine the antiatherogenicity of HDL. This review presents current views on the molecular mechanisms underlying these three, previously-mentioned, most studied antiatherogenic functions of HDL through the analysis of genetically-engineered mice.

3. HDL AND REVERSE CHOLESTEROL TRANSPORT (RCT)

3.1. Mechanisms

HDL plays an important role in cholesterol homeostasis by promoting cholesterol efflux from peripheral cells and delivering that cholesterol to the liver, from where it will be partly eliminated through the biliary pathway, a process termed reverse cholesterol transport (RCT). Cholesterol efflux from cells is the combined result of a non-specific and passive efflux as well as a specific and active process, with the latter being mediated by ATP-binding cassette (ABC) transporters (2, 21, 22). It is generally thought that the interaction produced between prebeta-HDL and ABCA1, or other members of the ABC protein group, induces cholesterol translocation from the cytoplasm to the cell membrane (2). Three types of prebeta-HDL exist. The prebeta1 are the smallest particles and those which first receive cell cholesterol. After a few minutes, the cholesterol passes to prebeta2 and prebeta3, which are particles with increasingly greater size. Cholesterol in these nascent discoidal particles are then esterified by lecithin:cholesterol acyltransferase (LCAT). This esterification process is a key step for maintaining the gradient of free cholesterol and enabling HDL to be an acceptor of cholesterol. Finally, cholesteryl esters formed in HDL can be: i) taken up selectively from HDL after their binding to the scavenger receptor type BI (SR-BI) in liver, gonads and adrenal glands, ii) captured by tissues together with the whole HDL particle, especially in liver and kidney, and; iii) transferred by CETP to apoB-containing lipoproteins which are later cleared by the liver via receptor-dependent pathways such as low-density lipoprotein receptor (LDLR), very-low-density lipoprotein (VLDL) receptor and LDLR-related protein (LRP). Genes and their products involved in HDL-mediated RCT are shown in Figure 1.

Although the role of many genes in individual steps in the RCT pathway has been studied in detail (2), little is known on how these genes regulate cholesterol efflux through the entire pathway. Various efforts have been made to quantify overall RCT in genetically-modified mice. One approach was to quantify overall RCT by measuring peripheral cholesterol synthesis, which in the steady state approximates the centripetal cholesterol efflux to the liver (23-25). Measurements of biliary lipid outputs or fecal sterol excretion have also been used to determine the relationship between HDL and the final excretion of biliary steroids through the liver (26). Recently, the injection of cationized LDL labeled with [^{3}H]cholesterol into the rectus femoris muscle and the rate of [^{3}H]cholesterol loss from the muscle depot was used to determine RCT *in vivo* (27). The main obstacle to such studies has been the inability to specifically estimate RCT from macrophages, the most important cholesterol-loaded cells of atherosclerotic lesions (28). A novel approach has been developed to measure macrophage-specific RCT *in vivo* by tracing the reverse [^{3}H]cholesterol transport from macrophages to feces in mice (29). Of note, a recent report demonstrated that the increase in fecal sterol excretion mediated by liver X receptor (LXR) is independent of biliary cholesterol excretion in mdr2 P-glycoprotein knockout mice, suggesting the existence of an alternative RCT pathway through the intestine (30). A complete list of the pivotal genes involved in HDL metabolism and their effects on HDLc, RCT and atherosclerosis in genetically-engineered mice is shown in Table 1.

3.2. Genes and their products involved in RCT

3.2.1. Apo A-I

The pivotal role of apoA-I in the regulation of HDL metabolism is highlighted by the changes of HDLc in genetically modified mouse models. In mice, transgenic and somatic overexpression of apoA-I has a protective role against atherosclerosis (7-9, 31), and even induces the

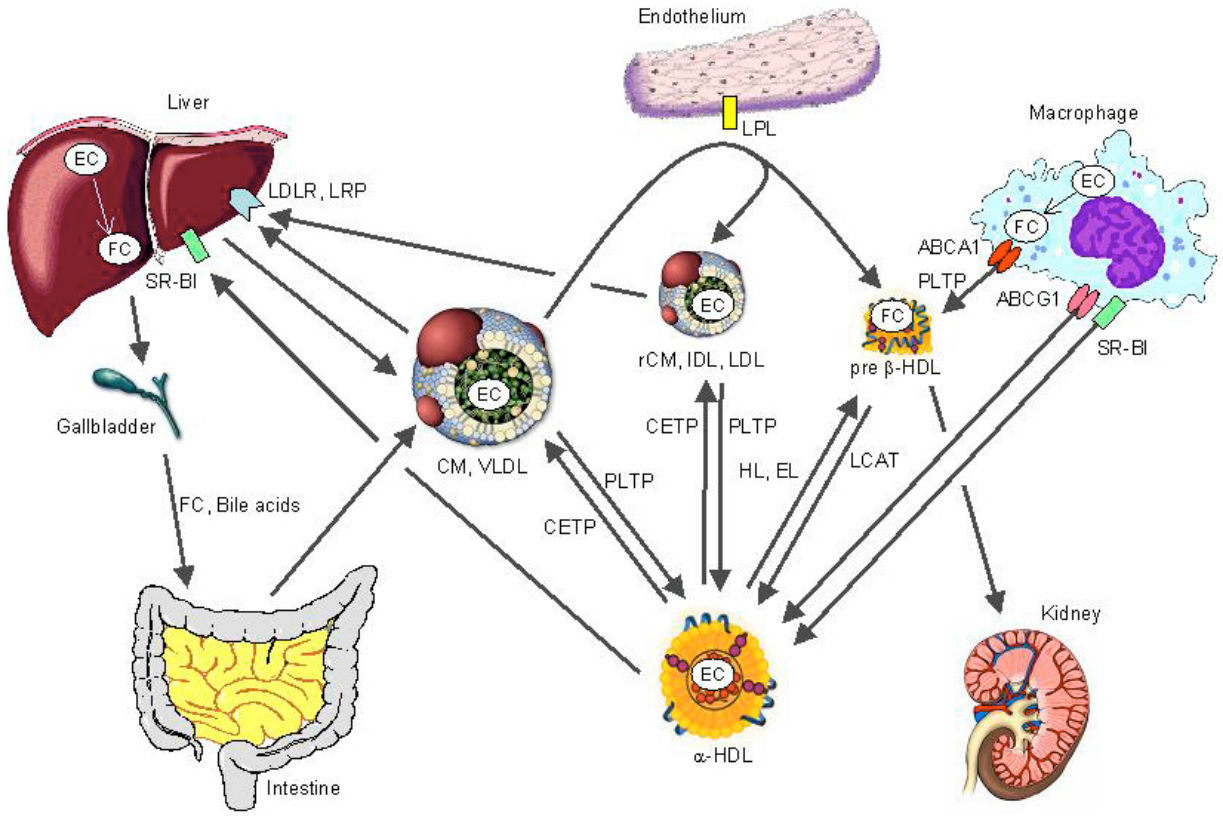

Figure 1. A schematic diagram of RCT from macrophages to feces in vivo. Nascent partially-lipidated prebeta-HDL particles acquire free cholesterol (FC) from peripheral cells by adenosine triphosphate-binding cassette transporter (ABC) A1. FC is converted into cholesteryl ester (CE) within the HDL particle by the enzyme lecithin-cholesterol acyltransferase (LCAT). The scavenger receptor class-BI (SR-BI) and ABCG1 may also facilitate the cholesterol efflux process from these cells to mature HDL. Hepatic lipase (HL) or endothelial lipase (EL) can hydrolyze HDL triglyceride (TG) and phospholipids, thereby remodeling larger HDL particles into smaller ones, which can then be catalyzed via the kidney. Lipoprotein lipase (LPL) contributes to HDL biogenesis by generating phospholipids and surface apolipoproteins that can be acquired by HDL. The liver can take selectively HDL-associated cholesteryl ester via SR-BI and excrete it into bile as free cholesterol (FC) or bile acids. HDL-CE can also be transferred to apoB-containing lipoproteins by the action of CE transfer protein (CETP) and returned to the liver through the low-density lipoprotein (LDL) receptor (LDLR) or the LDL related protein (LRP). PLTP=phospholipids transfer protein; CM=chylomicron; rCM= remnant chylomicron; VLDL=very-low-density lipoprotein; IDL=intermediate-density lipoprotein.

regression of preexisting lesions (32). Consistently, overexpression of apoA-I in mice resulted in an increased cellular cholesterol efflux capacity of plasma, the first step of RCT (2, 33). These data suggested that stimulated production of apoA-I enhanced RCT and protected from atherosclerosis. However, overexpression of apoA-I in mice does not perturb the net centripetal flow of cholesterol from peripheral tissues to the liver (23, 24). Further, no evidence of increased loss rate of [^{3}H]cholesterol from a muscle depot was found in human apoA-I transgenic mice (34). The tracing of reverse [^{3}H]cholesterol transport from macrophages to feces in mice overexpressing apoA-I has provided direct evidence of a major antiatherogenic mechanism for apoA-I (29). Thus, while apoA-I does not bear a simple relationship with overall centripetal RCT, it is certainly rate-limiting for macrophage-specific RCT *in vivo*. One probable mechanism of action is the enhancement of the macrophage ABCA1-mediated cholesterol efflux produced by increased free apoA-I. Further, several recombinant peptides with aminoacid sequences that mimic the structure of apoA-I have antiatherogenic effects in mice (35-37) and the apoA-I mimetic peptide D-4F enhanced cholesterol efflux from macrophage cell cultures and macrophage-specific RCT *in vivo* (38). Interestingly, the injection of apoA-I into mice also resulted in increased ABCA1 protein levels in macrophages and liver (39). ApoA-I knockout mice did not develop more atherosclerosis than controls (15); however, an increase was observed in atherosclerosis susceptibility in apoA-I-deficient hypercholesterolemic mice (apoA-I/LDLR double knockout mice and apoA-I knockout mice overexpressing human apoB-100) (40, 41). These data support the concept that the increase in apoA-I prevents atherosclerosis, but its deficiency does not necessarily favor atherosclerosis development unless other risk factors exist (2). The relationship between apoA-I deficiency and RCT

Table 1. Modification of HDL-related genes in experimental mice. Effects on HDLc, RCT, antioxidant activity and atherosclerosis

Gene	Modification	HDLc	Centripetal RCT	RCT from muscle depot	Biliary lipid excretion	Macrophage-specific RCT	Antioxidant activity	Atherosclerosis	Reference
Human apoA-I	Transgenic	Increased		Unchanged			Increased	Decreased	7, 34, 208
Human apoA-I	Adenovirus-mediated overexpression	Increased	Unchanged			Increased			24, 29
Mouse apoA-I	Knockout	Decreased	Unchanged	Decreased	Unchanged		Decreased	Unchanged or Increased	15, 25, 40-43, 213
Mouse apoA-II	Transgenic	Increased					Decreased	Increased	51, 68
Human apoA-II	Transgenic	Decreased				Unchanged	Decreased	Increased	52, 54, 69
Human apoA-IV	Transgenic	Increased		Unchanged			Increased	Decreased	76, 77, 245
Human ABCA1	Transgenic	Increased			Increased			Decreased	86, 91
Mouse ABCA1	Knockout	Decreased			Unchanged			Unchanged	92, 94
Mouse ABCA1	Macrophage-specific inactivation	Unchanged				Decreased		Increased	95
ABCG1	Adenovirus-mediated overexpression	Decreased			Increased				102
Mouse HL	Knockout	Increased			Unchanged			Decreased	120, 121
Human LCAT	Transgenic	Increased			Unchanged			Increased, decreased or unchanged	131-135
LCAT	Adenovirus-mediated overexpression	Increased	Unchanged				Increased		24, 239
LCAT	Knockout	Decreased					Decreased	Increased or decreased	136-138
Simian CETP	Transgenic	Decreased	Unchanged	Unchanged				Increased	23, 145, 147
Human CETP	Transgenic	Decreased	Unchanged					Increased	24, 148
Human PLTP	Transgenic	Decreased			Increased		Decreased	Increased	154, 157, 160
Mouse PLTP	Knockout	Decreased					Increased	Decreased	156, 249
Human SR-BI	Transgenic	Decreased	Unchanged		Increased			Decreased	24, 178-180, 183
Mouse SR-BI	Knockout	Increased			Decreased			Increased	172-174
Human PON1	Transgenic	Unchanged					Increased	Decreased	227, 228
Mouse PON1	Knockout	Unchanged					Decreased	Increased	224, 225
Human PAF-AH	Adenovirus-mediated overexpression	Unchanged					Increased	Decreased	230, 231
Human sPLA2	Transgenic	Decreased					Decreased	Increased	243

is uncertain. Plasmas of apoA-I knockout mice have half-normal cholesterol efflux capacity, and lack of apoA-I in knockout mice results in a delay in [^{3}H]cholesterol loss from a localized depot *in vivo* (42). However, centripetal cholesterol efflux and net steroid excretion were not appreciably changed in apoA-I knockout mice (25, 43), whereas there have been no reports on macrophage-specific RCT in these mice.

ApoA-I Milano (apoA-IM) is a naturally occurring-mutant of apoA-I that has been identified in a number of subjects in Northern Italy where it is associated with low HDLc (44). The apolipoprotein A-IM is a molecular variant of apoA-I characterized by an arginine-to-cysteine substitution at position 173 (45). Reconstituted HDL (rHDL) containing the ApoA-IM dimer were significantly more efficient in promoting cholesterol efflux from macrophages than the corresponding particle containing wild-type apoA-I, thus supporting an active role of the dimer in the first step of RCT (46). Consistently, infusion of apoA-IM in hypercholesterolemic apoE-deficient mice reduced the plaque lipid and macrophage content of aortic root atheromas (47, 48). Further, ApoA-IM improved endothelial dysfunction which was associated with mobilization of aortic cholesterol (49). Recently, a pilot clinical study also demonstrated a significant regression of atherosclerosis in human coronary arteries after ApoA-IM infusion (50). An important drawback of this study is the lack of a direct comparison between wild-type apoA-I and apoA-IM.

3.2.2. Apo A-II

Overexpression of mouse apoA-II has been found to be pro-atherogenic (51). Human apoA-II transgenic mice

have also generally been found to display increased atherosclerosis susceptibility, but exclusively when fed an atherogenic diet (52-54) or when cross-bred with apoE-deficient mice (apoE knockout) and fed a regular chow diet (55). The apoA-II locus has been suggested as an important genetic determinant of HDLc concentration, even though a major species-specific difference exists between the effects of mouse and human apoA-II (56-59). There is now some consensus that LpA-I is more active than LpA-I/A-II in cellular cholesterol efflux (56). ApoA-II exerted a negative effect on SR-BI-specific binding (60, 61) and on cholesterol selective uptake in some (60, 62), although not all, reports (61). Further, the level of apoA-II in HDL from apoA-II transgenic and apoA-II knockout mice was inversely correlated with HDL binding and selective cholesteryl ester uptake by both SR-BI and CD36 scavenger receptors (63, 64). Plasma from human apoA-II transgenic mice stimulated cholesterol efflux from ABCA1-expressing J774 macrophages (65), but decreased efflux from SR-BI-expressing Fu5AH hepatoma cells (65-67). Thus, a pro-atherogenic mechanism of apoA-II overexpression could involve reduced RCT (56, 59). However, overexpression of murine or human apoA-II in transgenic mice maintains effective cholesterol efflux from macrophages and macrophage-specific RCT *in vivo* (68, 69), suggesting that SR-BI-independent pathways (70, 71) may contribute to the enhanced uptake of HDL-derived cholesterol found in the liver of apoA-II transgenic mice and maintain RCT *in vivo* (63, 69).

3.2.3. Other proteins

ApoA-IV is synthesized mainly in the intestine and is associated with HDL (72). One of the main metabolic functions assigned to apoA-IV is that related to RCT. ApoA-IV is a potent activator of LCAT (73) and plasma from human apoA-IV transgenic mice can promote macrophage cholesterol efflux (74). Further, overexpression of murine or human apoA-IV in transgenic mice confered significant protection against atherosclerosis (75, 76). However, overexpression of human apoA-IV protected against atherosclerosis in apoE knockout mice without increases in HDLc (76), and high plasma levels of human apoA-IV did not enhance [^{3}H]cholesterol mobilization from a muscle depot *in vivo* (77). These results suggested that apoA-IV could protect against atherosclerosis by mechanisms that are independent of RCT (see section 4.2.7).

Several groups have demonstrated that transplantation of wild-type bone marrow or selective expression of a human apoE transgene in macrophages reduce atherosclerosis in apoE knockout mice (78-80). Since apoE expressed by macrophages in apoE knockout mice is too low to reduce hypercholesterolemia, the protection against atherosclerosis is likely to be due to apoE production by macrophages in the arterial wall leading to increased cholesterol efflux from these cells (2). However, the contribution of apoE to overall and macrophage-specific RCT *in vivo* remains to be established.

It has been shown recently that apoM knockout mice accumulated cholesterol in large HDL particles and this markedly reduced cholesterol efflux from macrophages to apoM-deficient HDL compared to normal HDL (81). Accordingly, overexpression of apoM in LDLR knockout mice protected against atherosclerosis when the mice were challenged with a cholesterol-enriched diet (81), suggesting that apoM is important for the formation of prebeta-HDL and could protect against atherosclerosis by mechanisms that are dependent of RCT.

An interesting study has demonstrated a role of caveolin-1 in regulating HDL metabolism. C57BL/6J mice were injected with adenoviruses encoding either caveolin-1 or green fluorescent protein together with a transactivator adenovirus (82). In caveolin-1 overexpressing animals, plasma HDLc levels were found to be approximately 2-fold elevated, as compared with control animals. Consistently, caveolin-1 inhibits DiI-HDL uptake mediated by SR-BI in primary cultures of hepatocytes (82). In addition, caveolin-1 expression increased the secretion of apoA-I in cultured hepatocytes and apoA-I plasma levels in mice (82). However, the effects of caveolin-1 on overall and macrophage-specific RCT are unknown.

3.2.4. ATP-binding cassette transporter A1 (ABCA1)

The ABCA1 has been identified as the defective molecule in Tangier disease, a rare disorder characterized by cholesterol accumulation in the reticuloendothelial system and markedly reduced HDLc levels (83-85). Several studies have determined that liver and intestine play a major role in the maintenance of plasma HDL levels and the biogenesis of nascent partially lipidated HDL particles, the main acceptors of cholesterol by ABCA1-mediated efflux from peripheral tissues (86-90). Overexpression of ABCA1 in liver and peripheral macrophages of transgenic mice resulted in increased HDLc levels and reduced atherosclerosis (86, 91). These transgenic mice presented a significant rise in the net hepatic delivery of exogenous radiolabeled cholesteryl ether HDL and biliary cholesterol excretion, indicating that activation of the ABCA1 transporter may facilitate RCT (86). However, no obvious effect on overall RCT in ABCA1 knockout mice was observed despite the expected absence of HDL. Hepatobiliary cholesterol transport was not impaired in ABCA1 knockout mice (92), and the increased hepatobiliary and fecal cholesterol excretion upon activation of the LXR was independent of ABCA1 (93). Further, the expected increase in atherosclerosis in ABCA1 knockout mice was not observed (94). Recently, experiments in which ABCA1 was selectively inactivated in macrophages have provided a clue to these inconsistencies. Selective inactivation of ABCA1 in macrophages markedly enhanced aortic atherosclerosis in hyperlipidemic strains of mice in absence of any changes in plasma HDL levels (95). One possible explanation is that the excessive uptake of cholesterol by ABCA1-deficient macrophages in the artery wall could not be compensated by the ABCA1-mediated efflux in these mice. In favor of this, we found a reduced RCT from cholesterol-loaded ABCA1-deficient macrophages to feces in ABCA1 knockout mice (Calpe-Berdiel et al., unpublished results). These studies also indicate that macrophage cholesterol, although important for atherosclerosis, does not provide a significant proportion of HDLc (95). Consistently, liver-

specific ABCA1-knockout mice presented decreased levels of HDLc (96).

3.2.5. Other ATP-binding cassette transporters

ABCG1 is primarily expressed in both macrophages and endothelial cells. It is upregulated in response to cholesterol loading in the macrophage (97-99). ABCG1 can promote cholesterol efflux from vascular cells to HDL (100, 101). ABCG1-deficient mice exhibited a massive accumulation of neutral lipids and phospholipids in hepatocytes and in macrophages within multiple tissues following administration of a high-fat, high- cholesterol diet, with no effects on plasma HDL. ABCG1 transgenic mice were protected from this accumulation (101). Overexpression of ABCG1 in the liver of mice using recombinant ABCG1 vectors resulted in decreased plasma HDL levels and increased biliary cholesterol excretion (102). Therefore, these results suggest a potential role for ABCG1 as a mediator of cholesterol efflux from macrophages to mature HDL in some tissues and in overall RCT.

ABCG4 is also important in the process of cholesterol efflux (100), however taking into account that ABCG4 is highly expressed in brain (103), its role in RCT is considered uncertain.

3.2.6. Lipoprotein lipase (LPL)

LPL is bound to the endothelial surface and is abundant in adipose tissue and muscle. This enzyme hydrolyzes chylomicron and VLDL-associated triglycerides to provide fatty acids to tissues as an energy source (104). The general characteristics of this protein are usually analyzed in relation to the metabolism of particles rich in triglycerides. Nevertheless, LPL activity is also essential for HDL production from triglyceride-rich lipoprotein catabolism. Overexpression of LPL in transgenic mice increases HDLc (105). Conversely, LPL knockout mice had severe hypertriglyceridemia and reduced HDLc (106, 107) and adenovirus-mediated expression of LPL in LPL-deficient mice is necessary and sufficient to promote HDL maturation (108). This is probably due to the fact that LPL acts on chylomicrons and VLDL, changing their cortex/core ratio, and these lipoproteins tend to recover their primitive relationship by breaking off pieces of cortex that will float in the density range of HDL. On the other hand, initial evidence established that LPL increases HDL-associated cholesteryl ester by hepatic and extrahepatic cells *in vitro* (109-111). In this regard, expression of human LPL in muscle of transgenic mice reduced plasma HDLc and increased the catabolism of HDL-associated cholesteryl ester (112), suggesting that LPL may facilitate RCT through the HDL-pathway *in vivo*. In contrast, macrophage LPL expression has been shown to enhance aortic lesion formation, probably by promoting lipoprotein internalization and lipid accumulation by macrophages (113, 114). The effects of LPL on overall and macrophage-specific RCT are unknown.

3.2.7. Hepatic lipase (HL)

HL is an enzyme belonging to the same family as LPL, and mainly hydrolyzes IDL and HDL-associated phospholipids and triglycerides. HL knockout mice showed increased HDLc and decreased selective uptake of HDL-cholesteryl ester (115). Liver overexpression of HL in transgenic mice decreased HDLc, induced the formation of smaller HDL particles and reduced atherosclerosis (116, 117). Further, overexpression of human HL enhanced the plasma clearance of HDL cholesteryl ester (118). These studies show that HL have a substantial impact on HDL metabolism *in vivo* and may play a central role in RCT in vivo. Apart from the role of HL in HDL metabolism, macrophage-specific HL expression may enhance aortic lesion formation by promoting lipoprotein internalization (119), thereby providing a potential explanation for the reduced atherosclerosis of HL/apoE double knockout mice (120). Only one work studied the relationship between HL and RCT *in vivo*. The deficiency of HL in knockout mice had no impact on the availability of lipoprotein-derived liver cholesterol for biliary secretion (121). Nevertheless, the effects of HL on macrophage-specific RCT have not been specifically addressed.

3.2.8. Endothelial lipase (EL)

EL is a member of the triglyceride lipase gene family and is more effective at hydrolyzing lipids from HDL than LPL and HL (122, 123). Liver overexpression of EL mediated by adenoviral gene transfer reduced HDLc and apoA-I in mice (124). Overexpression of EL in transgenic mice moderately reduced HDLc (125). Hepatic overexpression of EL increased the uptake of apoA-I from labeled HDL (126), suggesting that EL may facilitate late RCT events. Conversely, EL-deficiency in knockout mice and antibody inhibition of EL resulted in increased HDLc (125, 127, 128) and mouse EL inhibition increased HDL particle size and reduced HDL phospholipid turnover (127). However, aortic lesion area was reduced in EL/apoE double knockout mice despite a concomitant increase in apoB-containing lipoproteins (129). Those authors observed a decrease in macrophage content in the arterial wall of EL knockout mice and inhibition of monocyte adhesion *ex vivo* (129), suggesting alternative mechanisms by which EL may regulate atherogenesis. Further studies on the role of EL in RCT are required.

3.2.9. Lecithin:cholesterol acyltransferase (LCAT)

LCAT has been hypothesized as a potential therapeutic target for raising HDLc and modulating RCT (5, 13, 130). Adenovirus-mediated expression of LCAT in hamsters increased bile cholesterol excretion (131). In contrast, overexpression of LCAT in mice did not stimulate centripetal cholesterol efflux from any extrahepatic tissues or increase bile cholesterol and total bile acid excretion (24, 131). Overexpression of LCAT in transgenic mice has produced conflicting results on susceptibility to atherosclerosis (132-134), possibly because the antiatherogenic effects of LCAT require CETP activity (135). Either enhanced or reduced atherosclerosis was also shown in LCAT knockout mice despite an HDLc deficiency (136-138). Studies of RCT in LCAT deficiency have not been conducted. LCAT expression exerts various effects on lipoprotein metabolism, such as antioxidant activity (see section 4.2.5) and altered levels of apoB-containing lipoproteins, which may influence

atherosclerosis development (13, 130). It will thus be necessary to perform overall and macrophage-specific RCT analyses in the appropriate animal models to gain further insight into the role of LCAT in RCT and atherosclerosis.

3.2.10. Cholesteryl ester transfer protein (CETP)

The action of CETP results in a heteroexchange between HDL cholesteryl ester and VLDL- or chylomicron-triglycerides (139). Overexpression of human or simian CETP in transgenic mice, which naturally lack this activity, reduced HDLc (140-142) and increased preβ-HDL (143). The finding of a downregulation of LDLR expression in CETP transgenic mice was indicative of increased RCT to the liver (144). However, the magnitude of centripetal cholesterol from the periphery to liver was not altered in simian and human CETP transgenic mice (23, 24). Further, high levels of CETP in these mice did not enhance [^{3}H]cholesterol removal from a muscle depot but may act on extracellularly-located cholesteryl ester (145). The role of CETP in atherogenesis has mainly been studied in mice and has been shown to be complex (146). The introduction of human or primate CETP transgene in mice resulted in increased early aortic atherosclerotic lesions in response to an atherogenic diet (147, 148). Conversely, the expression of CETP transgenic mice in hypertriglyceridemic apoCIII transgenic or in LCAT transgenic mice reduced the area of atherosclerotic lesions (135, 148). Whether these differences can be explained by differential effects on macrophage-specific RCT or other HDL-related antiatherogenic properties remains unknown.

It is unclear whether humans with genetic CETP deficiency are protected from atherosclerotic cardiovascular disease or not (20, 149). However, several strategies have recently emerged to inhibit CETP and increase HDLc (13, 20). The CETP inhibitor torcetrapib was tested in humans and a 50-100% increase in HDLc was observed (150). JTT-705, another CETP inhibitor, was also proved to effectively increase HDLc in humans and rabbits (151, 152) and reduce atherosclerosis in rabbits (152). However, data on the anticipated reduction in atherosclerosis in humans, such as carotid intima media thickness or coronary atheroma volume, have yet to be reported.

3.2.11. Phospholipid transfer protein (PLTP)

PLTP facilitates the transfer of phospholipids between triglyceride-rich lipoproteins and HDL during lipolysis by LPL and modulates HDL size and composition (13, 153). Overexpression of human PLTP in transgenic mice lowers HDLc (154). Despite these low HDLc levels, these transgenic mice have increased generation of preβ-HDL and prevent macrophage cholesterol accumulation (154). However, PLTP knockout mice also showed low levels of HDLc (155). These intriguing observations may be explained by the reduced apoB-containing lipoproteins found in PLTP knockout mice and a loss of transfer of all major phospholipid classes from VLDL to HDL (155, 156). Two recent studies investigated the effect of increased PLTP activity on removal of cholesterol from the body of mice. Overexpression of human PLTP in transgenic mice increased biliary bile acid and increased the amount of fecal bile acids (157). The decrease in HDLc found in these transgenic mice may have been caused by accelerated clearance of HDL cholesteryl esters by the liver, as demonstrated with adenovirus-mediated overexpression of PLTP (158). Therefore, these results suggested that raised PLTP activity may have antiatherogenic effects via an enhanced RCT. However, PLTP transgenic mice showed increased atherosclerosis (159, 160). Conversely, PLTP deficiency reduced atherosclerosis in ApoB-transgenic and ApoE knockout mice (156). This may be related to reduced apoB production (13, 156) as well as reduced oxidant stress (see section 4.2.7).

3.2.12. Scavenger receptor-BI (SR-BI)

SR-BI is known to mediate the selective binding and bi-directional flux of cholesterol and other lipids between HDL and cells (161-164), particularly in hepatocytes and steroidogenic cells (165, 166). SR-BI is also expressed in macrophage foam cells in atherosclerotic plaques, endothelial cells, Kupffer cells in the liver and a variety of other cell types (163, 164, 167). The importance of SR-BI in HDL metabolism has been established by SR-BI gene manipulation in mice (163, 168, 169). SR-BI knockout mice presented increased HDLc levels, reduced selective HDLc clearance (170, 171), decreased bile cholesterol concentration and impaired biliary cholesterol secretion (172-174). Conversely, hepatic overexpression of SR-BI using recombinant adenovirus-mediated gene transfer or in transgenic mice resulted in decreased plasma levels of HDLc (175, 176), enhanced HDL cholesteryl ester clearance (175, 177, 178) and increased biliary cholesterol (176, 178, 179). These results suggested a critical role of hepatic SR-BI expression in RCT by controlling the utilization of HDLc for biliary secretion. However, overexpression of SR-BI did not affect centripetal cholesterol efflux from extrahepatic tissues to liver (24). Further, bile acid pool size and composition, fecal bile acid excretion and liver sterol synthesis were not affected in SR-BI knockout mice (174). It is not clear whether this lack of effect on centripetal and liver sterol synthesis was the result of compensatory pathways to maintain hepatic and extrahepatic cholesterol levels (24, 174). Whether SR-BI might facilitate biliary cholesterol secretion directly by mediating hepatic uptake of HDL cholesteryl ester or by participating in biliary cholesterol secretion from the canalicular membranes remains to be determined (174). Experiments in SR-BI transgenic and knockout mice have demonstrated the antiatherogenic activity of SR-BI (180, 181). Loss of SR-BI expression, in an apolipoprotein E-deficient background, accelerated the onset of atherosclerosis (172) and led to premature cardiovascular dysfunction (172, 182). Hepatic overexpression of SR-BI markedly reduced atherosclerosis in mice prone to the disease (180, 183). As mentioned above, expression of SR-BI in foam cells in the arterial wall may promote the initial step of macrophage-specific RCT (184). In favor of this, selective elimination of SR-BI expression in bone marrow-derived cells in LDLR knockout mice resulted in increased diet-induced atherosclerosis (185). In addition, SR-BI may facilitate RCT by enhancing the clearance of apoB-containing lipoproteins (175, 177, 186, 187). Interestingly, SR-B1 may change its functional role when serum amyloid A (SAA) is present. Thus, SAA-containing HDL isolated

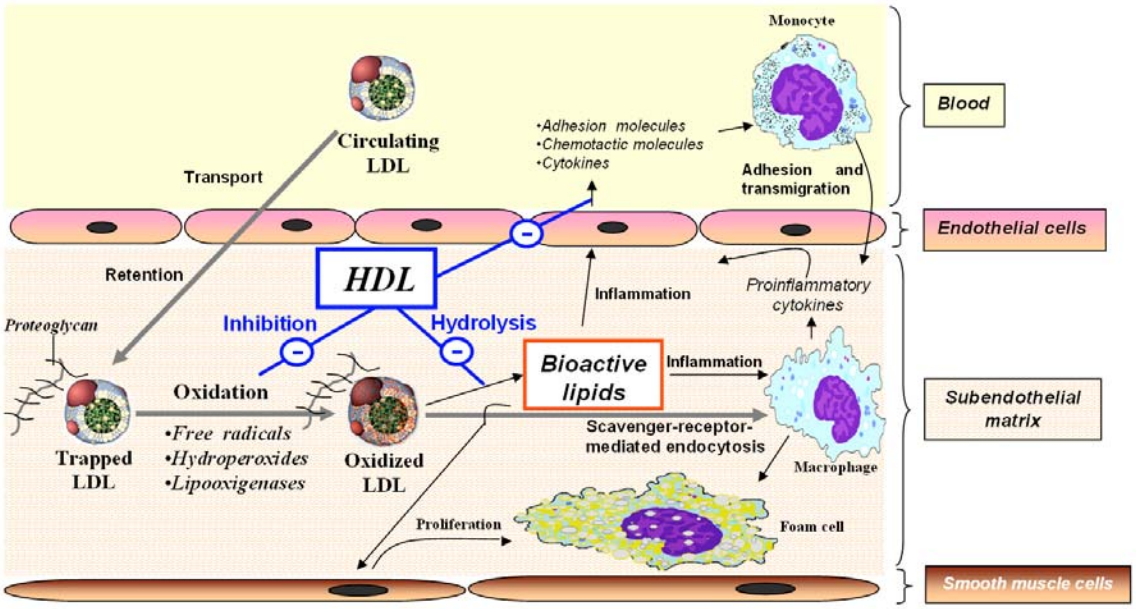

Figure 2. Current model of HDL antioxidant/anti-inflammatory action against atherosclerosis. Circulating LDL is transported through the endothelium and can be retained by proteoglycans in the subendothelial space. Trapped LDL may undergo oxidative modification triggered by hydroperoxides and free radicals derived from cell metabolism and enzymes such as lipooxigenases and myeloperoxidases. Oxidized LDL contains oxidized lipids, especially phospholipids, with proinflammatory effects that elicit a series of inflammatory responses in macrophages and endothelial cells. In addition, macrophages take up oxidized LDL in a process that converts them into foam cells, the hallmark cell of atherosclerosis. HDL has antioxidant and anti-inflammatory effects that may limit this process at several points. HDL inhibits the oxidative modification of LDL, and is able to inactivate proinflammatory oxidized lipids through its associated enzymes. HDL also inhibits the expression of endothelial chemotactic and cell adhesion proteins, thus reducing the infiltration of monocytes into the artery wall.

from mice overexpressing SAA through adenoviral gene transfer had little effect on HDL binding to SR-BI but decreased selective cholesteryl ester uptake (188).

4. ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIONS OF HDL

4.1. Mechanisms

In addition to its important role in promoting RCT, HDL is believed to protect against atherosclerosis by inhibiting the oxidative modification of low-density lipoproteins (LDL). Increasing evidence suggests that LDL oxidation plays a primary role in the initiation and progression of atherosclerosis. LDL trapped in the subendothelial space of the artery wall are subjected to oxidative modification via by-products of the lipooxygenase and myeloperoxidase pathways (189) and, probably, other prooxidant molecules derived from cell metabolism. Specifically, oxidation of arachidonic acid-containing phospholipids of LDL has been shown to yield specific proinflammatory products that elicit immune response in the arterial wall, including the induction of adhesion molecules and monocyte chemoattractants that facilitate foam cell formation (189). The *in vivo* proof of a role for the lipooxygenase pathway was provided by the generation of 12/15-lipooxygenase knockout mice. Deficiency of 12/15-lipooxygenase in an apoE- and LDLR-null background led to significantly less lipid peroxidation and decreased atherosclerosis (190-192). On the other hand, mouse models overexpressing 12/15-lipooxygenase have been shown to have increased lipid peroxidation and atherosclerosis (193, 194). HDL has been shown both to protect LDL against oxidation and to attenuate the biological activity of oxidized LDL. These antioxidant and anti-inflammatory properties of HDL have been attributed to the various proteins associated with HDL. Although antioxidant properties have been ascribed to apoA-I and apoA-II (195), it is currently believed that a significant part of HDL antioxidant properties are related to their associated enzymes: paraoxonase 1 (PON1) (196-198), PON3 (199, 200), platelet-activating factor acetylhydrolase (PAF-AH) (201) and LCAT (202) (see Figure 2 for a view of this hypothetical anti-atherogenic mechanism). Indeed, some of these enzymes have been found to be altered in atherosclerosis-susceptible strains of mice (203). A complete list of the pivotal genes involved in HDL antioxidant activity in genetically-engineered mice is shown in Table 1.

4.2. Genes and their products involved in antioxidative and anti-inflammatory actions of HDL

4.2.1. Apo A-I

In addition to its well-known role in RCT, already discussed, several studies indicate that apoA-I can inhibit various steps in the accumulation of oxidized lipids that promote inflammation and lead to atherosclerotic lesions. ApoA-I is able to remove oxidant LDL molecules protecting it from its oxidative modification, as shown by *in vitro* testing and by infusion of apoA-I in mice or human

(204). HDL is a major carrier of plasma lipid hydroperoxides in both mice and in humans (205), which are cleared faster by hepatocytes than non-modified lipids (206, 207), suggesting a key role of HDL in the metabolism of oxidant molecules. Isolated HDL from human apoA-I transgenic mice consistently prevents the oxidative modification of LDL more than HDL of control mice (208). These features may be an indication of a role of apoA-I in immunity, as HDL is one of the major blood components that bind to bacterial lipopolysaccharide (LPS) (209), and high HDL levels protect animals from LPS-induced septic shock (210). ApoA-I mimetic peptides reduced atherosclerosis when administered to apoE knockout mice and this effect was linked both to enhanced RCT and reduced lipid oxidation, independently of plasma cholesterol levels (35, 211). These studies suggest that synthetic peptides, such as native apoA-I, may act as anti-inflammatory agents in HDL (212). In addition to its ability to remove oxidant molecules from LDL and decrease the activity of hydroperoxides, it is believed that the main antioxidant/anti-inflammatory function of apoA-I is the transport and stabilization of antioxidant enzymes in HDL (195). These enzymes include PON1 and PAF-AH. Variability in PON activity correlates with HDLc and apoA-I, and this may reflect the stabilization of PON1 by apoA-I in the HDL particle. In apoA-I-deficient mice, PON1 was reduced by more than 60% and PON level was restored when these mice were injected with adenoviruses encoding human apoA-I (213). Conversely, human apoA-I transgenic mice showed increased PON1 and PAF-AH activities (214), supporting previous *in vitro* findings suggesting that PON activity is stabilized in the presence of the apolipoprotein, although apoA-I is not necessary for PON1 association with HDL (215). Of note, increases in apo A-I and HDL cholesterol inhibit foam cell formation in apo E–deficient/human apo A-I transgenic mice at a stage following lipid deposition, endothelial activation, and monocyte adherence, without increases in HDL-associated PON (216). In accordance with these findings, phospho-Akt, phospho-ERK1/2, and TGF-beta2 expression was increased in the aorta of human apoA-I transgenic mice compared with apoA-I-knockout mice (217). Further, phospho-Smad2/3 expression, the transcription factor activated by TGF-beta, was increased in transgenic mice (217). Thus, the results of the present work suggest a novel target for the antiatherosclerotic effect of HDL.

4.2.2. Apo A-II

HDL isolated from murine apoA-II transgenic mice was unable to protect against LDL oxidation by vascular cells (68), and this impaired ability to protect LDL against cell-mediated oxidation was attributed to lower PON activity in HDL particles of apoA-II transgenic mice. Similar results were found in a line of mice overexpressing human apoA-II with impaired HDL protection against oxidative modification of apoB-containing lipoproteins (54). In these transgenic mice, a decrease in apoA-I levels and PON and PAF-AH activity was related to this impairment and possibly contributed to their increased atherosclerosis susceptibility (54). The displacement of apoA-I and PON from HDL by human apoA-II could explain, at least in part, the decreased level of these proteins in this animal model (54) and, also, why PON is mostly found in HDL particles with apoA-I but without apoA-II. It has also been shown that substituting the central domain of apoA-I by a segment of human apoA-II in transgenic mice in an apoE-null background enhances oxidative stress and impairs the protection of HDL against LDL oxidative modification, without altering the plasma capacity of inducing cholesterol efflux (218). These studies suggest that apoA-II exerts, at least part of, its pro-atherogenic effect by counteracting the antioxidant properties of HDL (54, 68). Nevertheless, another line of independently-generated human apoA-II transgenic mice was reported to have HDL displaying a relatively increased protection against VLDL oxidative modification despite decreased HDLc, PON and PAF-AH (219). The reasons for this discrepancy are unclear.

4.2.3. Paraoxonase (PON)

PON1 is a calcium-dependent ester hydrolase (220) that catalyzes the hydrolysis of organophosphates and oxidized phospholipids (196, 221), including PAF (222). PON has been demonstrated to protect LDL against oxidation, reverse the biological effects of oxidized LDL and preserve the function of HDL by inhibiting its oxidation (223). These findings were confirmed *in vivo* in PON1-deficient mice. PON1 knockout mice exhibited no detectable plasma PON activity, and HDL from PON1-null mice was unable to protect LDL against oxidation in cultured cells of artery wall (224). In addition, PON1-null mice fed an atherogenic diet or crossed with apoE knockout mice showed increased atherosclerosis (225). Additionally, LDL freshly isolated from PON1/apoE double knockout mice had higher levels of biologically-active phospholipids and their HDL failed to protect LDL against oxidation (225). PON1 may also reduce oxidative stress in macrophages, as described in studies with PON1 knockout mice (226). Conversely, PON1 transgenic mice presented increased PON activity in their HDL particles without altering their composition or size, and isolated HDL from these mice was more resistant to lipid peroxidation compared with HDL from their control littermates (227). HDL isolated from human PON1 transgenic mice exhibited an enhanced ability to protect LDL against oxidation (227). Moreover, comparing with their control littermates, human PON1 transgenic mice developed significantly smaller lesions in both C57BL6 and apoE-null backgrounds (228). Further, human PON was also expressed in macrophages and reduced macrophage and aortic oxidative status (229). This may also explain their attenuated atherosclerosis development (229). These studies corroborate the hypothesis that PON1 protects against atherogenesis and it is an important contributor to the antioxidant capacity of HDL.

4.2.4. Platelet activating factor acetylhydrolase (PAF-AH)

PAF-AH is a type VIIA phospholipase associated with HDL in mice that hydrolyzes the acetyl moiety of the sn-2 position of PAF and, also, oxidizes phospholipids with short-chain acyl moieties in the sn-2 position. To date, no PAF-AH knockout or transgenic mice have been developed, but some studies have used somatic gene

transfer. Adenoviral gene transfer of human PAF-AH in apoE knockout mice reduced macrophage homing to endothelium by decreasing oxidative stress (230). Also, intravenous administration of an adenovirus directing a liver-specific expression of human PAF-AH in apoE-deficient mice resulted in decreased oxidized lipoproteins, inhibition of injury-induced neointima formation and spontaneous atherosclerosis (231). Using this approach, human PAF-AH bound to all mouse lipoproteins and protected them from oxidation, thereby decreasing lipid oxidation and preserving HDL functions (232). Transfer of PAF-AH into skeletal muscle in apoE-deficient mice was also associated with a reduced extent of atherosclerosis (233). ApoE knockout mice presented reduced levels of PAF-AH and this was concomitant with increased levels of circulating oxidized phospholipids (203). Apparently, PAF-AH could act in cooperation with PON in LDL protection against oxidative modification, as suggested by the fact that PON1 knockout mice presented impaired HDL protection against LDL oxidation despite normal PAF-AH activity (224). In contrast, a growing number of epidemiological studies in humans suggest that increased PAF-AH is an independent predictor of cardiovascular events (234, 235). This may be related to the close association of PAF-AH with atherogenic dense LDL particles (236, 237). The PAF-AH-mediated formation of noxious bioactive lipid mediators has been proposed to explain this potentially proinflammatory role of PAF-AH in humans (235). Therefore, functional evaluation of PAF-AH in mice is hindered by the predominant association of PAF-AH with HDL, thereby protecting LDL from oxidative modification and atherosclerosis development.

4.2.5. Lecithin:cholesterol acyltransferase (LCAT)

Although the main known function of LCAT is cholesterol esterification, a role of LCAT in hydrolyzing oxidized polar phospholipids generated during lipoprotein oxidation has also been described (202, 238). Transient LCAT overexpression was associated with decreased oxidative stress and atherosclerosis in LDLR knockout and leptin-deficient (ob/ob) double-mutant mice (239), thus supporting an antioxidant role of LCAT *in vivo*. Further, LCAT function in HDL metabolism is also important for maintaining its antioxidant/anti-inflammatory potential, since LCAT-targeted disruption in mice was associated with HDL deficiency, leading to dramatic reductions in apoA-I, PON and PAF-AH (240). However, the oxidative stress found in LCAT-deficient mice was paradoxically reversed in apoE knockout mice, possibly due to redistribution of PON to apoB-containing lipoproteins (138).

4.2.6. Type IIa secretory phospholipase (sPLA2)

Several studies suggested the implication of sPLA2, an HDL-associated protein, in atherogenesis. C57BL/6 mice, which are commonly used to study atherosclerosis, have a point mutation in the sPLA2 gene that renders the enzyme nonfunctional (241). When C57Bl/K mice, with intact sPLA2 were crossed with apoE knockout mice, the resulting apoE-null sPLA2+/+ mice showed no difference in atherosclerosis susceptibility compared the double knockout mice (242). In contrast, human sPLA2 transgenic mice showed reduced HDLc and dramatically increased atherosclerotic lesions on both low-fat and atherogenic diets. In addition, oxidized phospholipids levels were increased and HDL from transgenic mice showed decreased PON levels failing to protect LDL from oxidation (243). Specific overexpression of sPLA2 in macrophages also resulted in accelerated atherogenesis associated with in vivo oxidative stress, without affecting systemic sPLA2 activity or lipoprotein metabolism (244). These observations indicate that overexpression of the active enzyme in macrophages promotes atherosclerosis in hypercholesterolemic mice, suggesting that local expression of the enzyme in the artery wall might be atherogenic.

4.2.7. Other factors related to oxidative and anti-inflammatory protection of HDL

In addition to the role of apoA-IV in RCT, it has been suggested that apoA-IV acts *in vivo* as an antioxidant in human apoA-IV transgenic/apoE knockout mice thereby decreasing the progression of atherosclerosis (245). Further, apoA-IV knockout mice exhibited a significantly greater inflammatory response to 3% dextran sulfate sodium (DSS) acute colitis and this greater susceptibility to DSS-induced inflammation was reversed upon exogenous administration of apoA-IV to knockout mice (246). This anti-inflammatory effect likely involves the inhibition of P-selectin-mediated leukocyte and platelet adhesive interactions (246). These results provide the first direct support for the hypothesis that apoA-IV is an endogenous anti-inflammatory protein.

A subset of HDL-PON particles in humans is associated with a unique protein termed "clusterin" or apoJ (247). Further, apoJ-deficient mice showed an accelerated development of immune complex lesions localized to the mesangium and induced by unilateral nephrectomy-induced hyperfiltration (248). These results support the hypothesis that apoJ/clusterin modifies immune complex metabolism and disposal.

PLTP could also have actions on HDL antioxidant/anti-inflammatory properties. Hence, it has been described that HDL from PLTP knockout mice had improved anti-inflammatory properties and reduced the ability of LDL to induce monocyte chemotactic activity (249), and this could explain, at least in part, the reduced atherosclerosis in PLTP knockout mice. In favor of this, adenovirus-mediated PLTP overexpression in apoE knockout mice resulted in increased atherosclerotic lesions and autoantibodies against oxidized apoB-containing lipoproteins (250), and overexpression of human PLTP in transgenic mice induced a dose-dependent increase in atherosclerosis and a decrease in PON and PAF-AH activities, despite reduced apoB-containing lipoproteins (160). Taken together, these studies support the concept that PLTP activity has negative effects on antioxidant defense against atherosclerosis.

5. NITRIC OXIDE-MEDIATED EFFECTS OF HDL ON ENDOTHELIUM

In addition to RCT and the antioxidative and anti-inflammatory properties of HDL, other actions have been

postulated to explain the antiatherogenic role of HDL. These include anticoagulant, antiaggregant and profibrinolytic activities that are mediated by the different components of HDL (17, 251, 252). However, most of these studies were performed *in vitro* (17, 252). Recent studies in both cultured cells and mice indicate that HDL is an autonomous protective factor for endothelium. Early endothelial dysfunction in atherosclerosis is characterized by a decrease in nitric oxide (NO) bioavailability and increased affinity for leukocytes, which is accompanied by increased apoptosis of endothelial cells in subsequent stages. Native HDL has been found to activate endothelial nitric oxide synthase (eNOS) in cultured endothelial cells, thus stimulating NO release (253, 254). In mice, exogenous native HDL produces vascular relaxation and this response is blocked by pre-treatment with nitro-L-arginine methyl ester (L-NAME), an eNOS antagonist (253). Heterologous expression studies with Chinese hamster ovary cells have revealed that SR-BI mediates the effects of HDL on eNOS activity (253). Thus, transient transfection of CHO cells with eNOS caused a significant increase (four-fold) in enzyme activity only when cultured cells stemmed from animals stably transformed with murine SR-BI (253). Vascular NO-dependent relaxation was only produced in isolated aortas of wild-type mice, but not in those of homozygous SR-BI knockout mice (253). Further, the response of eNOS to HDL in isolated plasma membranes is blocked by antibodies directed to apoA-I and SR-BI, but not to apoA-II, suggesting that HDL activates eNOS through an SR-BI interaction in a process that requires apoA-I binding (253). Further studies have revealed that the HDL-induced eNOS activation seems to be brought about by tyrosine and PI3 kinases, which eventually mediate human eNOS phosphorylation at serine 1177 by Akt kinases (255). Analysis of the lysosphingolipid receptor S1P3 knockout mice has demonstrated that S1P3 acts as a functional HDL receptor and has suggested that the vasodilatory effects of the HDL-associated lysophospholipids are mainly mediated by this receptor in cooperation with SR-BI (256, 257).

6. SUMMARY AND PERSPECTIVE

HDL metabolism and its relationship with atherosclerosis is a complex topic. Epidemiological studies have demonstrated that increased HDL is a protective factor against atherosclerotic cardiovascular disease. In contrast, familial hypoalphalipoproteinemia is associated with varying but usually increased atherosclerotic vascular disease. Significant advances have been produced by the development and detailed analysis of genetically-engineered mice. Recent studies suggest that macrophage-specific RCT induction may be more related to atherosclerosis than total RCT. Further, it is increasingly evident that the antioxidant function of HDL constitutes a major antiatherogenic protective HDL property. Inhibition of LDL oxidation by HDL may be attributed to the presence of PON and PAF-AH, which prevent LDL oxidation. Further, the antioxidant properties of HDL are related to the presence of apoA-II and apoA-IV and the action of other enzymes such as LCAT, PLTP and sPLA2.

ApoA-I, the main apolipoprotein of HDL, has clear effects on RCT, protection against LDL oxidative modification and NO-dependent vasorelaxation. It is therefore not surprising that great efforts have been made to identify agents that can upregulate apoA-I expression or mimic its effects. Hence, one possibility of treating or preventing atherosclerotic cardiovascular disease would be to administer native or mutated apoA-I (such as apoA-I Milano) or mimetic peptides, as demonstrated in mouse models of atherosclerosis and, more recently, in humans. Experiments with genetically-modified mice also suggest that overexpression of pivotal genes in RCT, such as ABCA1 and SR-BI, exerts atheroprotective effects in mice. However, the role of apo A-II, apoA-IV, apoE, ABCG1, LPL, HL, EL, LCAT, CETP and PLTP on RCT or atherosclerosis remains a matter of debate or has not been proved to be antiatherogenic. An important lesson from these experiments is that disruption of RCT or antioxidant properties of HDL may result in atherosclerosis in the presence of either decreased, increased or unchanged HDLc.

It is therefore reasonable to believe that accumulated knowledge on HDL metabolism and its relationship with atherosclerosis in mice, though incomplete, holds promise for future therapeutic intervention in humans. The next decade could thus witness major advances in the development of therapeutic strategies that exploit the antiatherogenic properties of HDL.

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