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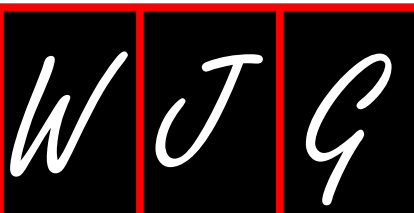
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Astrid van der Velde, PhD, Series Editor

## Reverse cholesterol transport: From classical view to new insights

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### Abstract

Cholesterol is of vital importance for the human body. It is a constituent for most biological membranes, it is needed for the formation of bile salts, and it is the precursor for steroid hormones and vitamin D. However, the presence of excess cholesterol in cells, and in particular in macrophages in the arterial vessel wall, might be harmful. The accumulation of cholesterol in arteries can lead to atherosclerosis, and in turn, to other cardiovascular diseases. The route that is primarily thought to be responsible for the disposal of cholesterol is called reverse cholesterol transport (RCT). Therefore, RCT is seen as an interesting target for the development of drugs aimed at the prevention of atherosclerosis. Research on RCT has taken off in recent years. In this review, the classical concepts about RCT are discussed, together with new insights about this topic.

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**Key words:** Cholesterol; Excretion; Transport; Intestine; Liver

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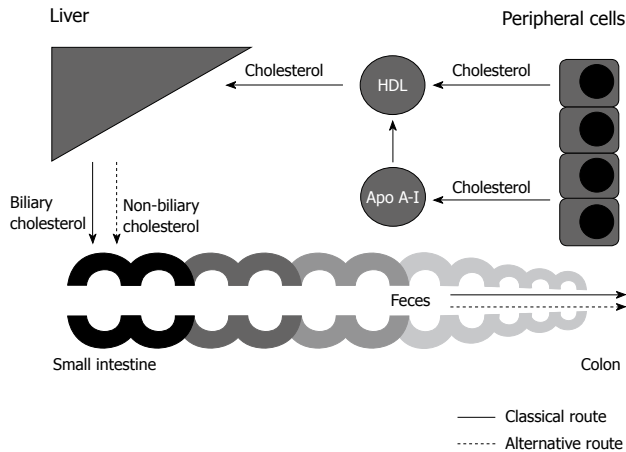
### INTRODUCTION

In order to dispose of cholesterol, it is transported from the periphery to the liver and intestine, and is finally excreted *via* the feces. This pathway has been traditionally referred to as reverse cholesterol transport (RCT) or centripetal cholesterol flux. In this review, the term RCT is used. Research on RCT has taken off in recent years. This review starts with introduction of the term RCT in the early 1970s. This is followed by a discussion of research in the following years that led to the classical view on RCT: high-density lipoprotein (HDL)-mediated transport of cholesterol from the periphery to the liver, the subsequent uptake of HDL cholesterol by the liver, hepatobiliary cholesterol secretion, and finally, excretion *via* the feces (Figure 1). Both free cholesterol and the esterified form are involved in RCT. Cholesteryl esters are much less amphiphatic than free cholesterol and appear to be the preferred form for transport in the plasma and for storage. The transport proteins involved in RCT receive special attention in this review. Finally, new insights in cholesterol excretion are discussed, which make the current concept of RCT questionable.

### THE BEGINNING

Glomset *et al*<sup>[1]</sup> introduced the term RCT in 1973, in a review that described the role of lecithin:cholesterol acyl





**Figure 1 Cholesterol excretion routes.** The filled arrows represent the classical route, and the dashed arrows represent the alternative route. In the classical view, apolipoprotein A-I (apo A-I) and high-density lipoprotein mediate cholesterol transport from the periphery towards the liver. Cholesterol is subsequently secreted into bile and is excreted via the feces. The alternative route describes the transport of non-biliary cholesterol towards the intestine for fecal excretion. How non-biliary cholesterol reaches the intestine is the subject of investigation.

transferase (LCAT) in metabolism. We nowadays know that LCAT is an enzyme that is synthesized in the liver and circulates in the blood plasma on the surface of lipoproteins, predominantly HDL. LCAT has the ability to catalyze the formation of cholesteryl esters on the surface of HDL by transferring fatty acids from phosphatidylcholine (PC, also known as lecithin) to the unesterified cholesterol<sup>[2]</sup>. It took several years after the discovery of LCAT before its physiological role was elucidated in more detail<sup>[3]</sup>. The *in vitro* testing of the possibility that LCAT plays a role in cholesterol transport was mainly hampered by the fact that most of the cholesterol of freshly prepared plasma lipoproteins is already esterified, that is, if the enzyme is able to alter the structure and physical properties of lipoproteins, most of the alterations have already occurred *in vivo*. The discovery of patients with familial LCAT deficiency<sup>[4-6]</sup> has provided a unique opportunity to circumvent these problems. By studying these patients, our knowledge about LCAT and cholesterol removal has increased.

## CLASSICAL VIEW

### Transport of cholesterol towards the liver

Although tissue culture studies had favored HDL<sup>[7,8]</sup> as the principal vehicle for cholesterol transport from the periphery to the liver, it took a decade before *in vivo* evidence was presented by Miller *et al*<sup>[9]</sup>. When cholesterol-loaded macrophages are incubated in medium that contains plasma, cholesterol moves from the cells to HDL and is subsequently esterified by LCAT<sup>[10]</sup>. The accumulation of cholesteryl esters in these particles increases their size and decreases their density; enrichment with apoprotein E also occurs, which decreases electrophoretic mobility<sup>[11,12]</sup>. Miller *et al*<sup>[9]</sup> have shown that similar changes were present in the circulating HDL of rabbits, when their peripheral

tissues were loaded with cholesterol by intravenous injection of acetylated or native human low-density lipoproteins (LDLs).

### Hepatic cholesterol uptake

Evidence for the existence of receptors that recognize HDL in plasma membranes of hepatocytes has been presented by several groups<sup>[13-15]</sup>. It appears that the rate of uptake of HDL cholesteryl esters by the liver in rats is several times greater than that of HDL apolipoprotein A-I (apo A-I), which suggests that cholesteryl esters dissociate from HDL particles at the surface of hepatocytes. This process might be facilitated by transient binding of HDL to the plasma membranes of such cells<sup>[16]</sup>. A similar process has been studied in cultures of human hepatoma cells<sup>[17]</sup>. The pathways for delivery of cholesteryl ester to the liver clearly cannot operate in patients with familial LCAT deficiency. Nevertheless, such patients do not accumulate large quantities of cholesterol in their plasma, as might be expected if the delivery of cholesteryl ester to the liver were hampered<sup>[18]</sup>.

### Hepatic processing of cholesterol

Once cholesterol has reached the liver, conversion into bile salts is the final destination for most of the cholesterol<sup>[19]</sup>. In contrast to cholesterol, bile salts are amphiphatic. Bile salts function as signaling molecules, and they act as physiological detergents: they emulsify droplets of dietary lipids in the intestine, which makes them available for absorption. Synthesis of bile salts involves the action of multiple different enzymes and can follow two major pathways, named the "classic" or neutral pathway and the alternative or acidic pathway. The classic pathway accounts for the majority of bile salt synthesis. In the enterohepatic circulation, intestinal bacteria modify bile acid structures, which yields secondary bile salts, for example, lithocholate and deoxycholate<sup>[20]</sup>. As about 95% of the bile salts re-enter the enterohepatic circulation, the bile salt pool of the body consists of a mixture of primary and secondary bile salts. Only a small part of hepatic cholesterol is not converted to bile salts and is directly secreted into bile. The majority of this hepatobiliary secreted cholesterol will be re-absorbed in the small intestine<sup>[21]</sup>.

### Lipoproteins and lipid transfer

The first evidence that HDL is not a homogeneous set of molecules, but rather a mixture of heterogeneous subclasses, arose in 1979. Gebhardt *et al*<sup>[22]</sup> have described the existence of a pre- $\beta$  migrating subclass of apo A-I-containing particles when studying human amniotic fluid. Similar particles have been demonstrated in peripheral lymph of dogs<sup>[23,24]</sup> and in human lymphedema fluid<sup>[25]</sup>. Castro *et al*<sup>[26]</sup> have found that, when radiolabeled cholesterol effluxes from cultured human fibroblasts into medium that contains human serum, almost all of it enters a minor component of HDL that is composed of very small apo A-I-containing particles. These particles differ from the majority of plasma HDL in having pre- $\beta$  elec-

trophoretic mobility on agarose gel. It is rich in phospholipids, and contains little or no core lipid, and apo A-I as the only recognized apoprotein<sup>[26-28]</sup>. We know now that it is pre- $\beta$  HDL cholesterol that is esterified by LCAT. After esterification, cholesteryl esters are sequestered into the core of the lipoprotein particle, eventually making spherical  $\alpha$ -HDL. In this way, cholesterol is made ready for removal<sup>[2]</sup>.

Some cholesteryl esters from HDL particles is transferred to LDL, very-low-density lipoproteins, or chylomicrons in exchange for triglycerides and phospholipids<sup>[29-35]</sup>. Triglyceride transfer is mediated by the cholesterol ester transfer protein (CETP) and phospholipid transfer is mediated by the phospholipid transfer protein (PLTP)<sup>[35,36]</sup>. Rodents do not express CETP, which might partly explain the high plasma HDL levels observed in these animals, in comparison to humans who express CETP. PLTP has not only been implicated in the transfer of phospholipids to HDL, but also in a process called HDL conversion<sup>[37]</sup>. In this process, PLTP mediates fusion of intermediate sized  $\alpha$ -HDL particles to generate larger HDL particles with a concomitant release of lipid-poor apo A-I. These actions result in an enhanced capacity to take up cellular cholesterol.

### Transport proteins

In the 1990s, several proteins and receptors involved in RCT were identified, which has given new insights in the mechanisms behind RCT.

**ABCA1:** Tangier disease was originally described and named on the basis of kindred living in Tangier Island in Chesapeake Bay, USA. Assmann *et al*<sup>[38]</sup> and Brook *et al*<sup>[39]</sup> have linked Tangier disease with abnormal HDL levels. The inheritance of the disease was already described in 1964<sup>[40]</sup>. However, it took until 1999 before it became clear that mutations in the ABCA1 (nowadays in humans and rodents referred to as ABCA1) gene were responsible for the severe HDL deficiency in Tangier disease<sup>[41-43]</sup>. We now know that ABCA1 is involved in the first step of RCT. The mechanism by which ABCA1 mediates cholesterol efflux has been a matter of intense investigation. Two distinct mechanisms have been proposed to explain ABCA1-mediated cholesterol efflux from macrophages to apo A-I. These models are described below.

One model argues that apo A-I binds ABCA1 at the plasma membrane and is subsequently internalized and targeted to intracellular compartments, where lipidation of apo A-I occurs as part of a retroendocytosis pathway<sup>[44-46]</sup>. Hassan *et al*<sup>[47]</sup> have shown that two-thirds of apo A-I is bound to the plasma membrane and one-third is found in intracellular compartments. It appears that the C-terminal region of apo A-I is important in the ABCA1-mediated lipid efflux pathway. Apo A-I dissociated four-fold faster from the intracellular compartments than from the plasma membrane, which suggests an important contribution of ABCA1 in the endocytic pathway to apo A-I lipidation. In contrast, Faulkner *et al*<sup>[48]</sup> have shown, by

studying ABCA1-mediated cholesterol efflux from macrophages, that the internalized apo A-I is re-secreted as a degraded protein. Furthermore, they have demonstrated that lipid-free apo A-I-mediated cholesterol efflux from macrophages could be pharmacologically uncoupled from apo A-I internalization into cells, which raises doubts as to the significance of the endocytic pathway in efflux. In addition, confocal microscopy and efflux assays of apo A-I internalization and lipidation as a function of ABCA1 expression have indicated that apo A-I lipidation occurs at the cell surface, whereas ABCA1-dependent apo A-I internalization leads to its lysosomal targeting and degradation<sup>[49]</sup>. Data of Azuma *et al*<sup>[50]</sup> have suggested that the retroendocytosis pathway of ABCA1/apo A-I contributes to HDL formation when excess lipoprotein-derived cholesterol has accumulated in cells.

The other model argues that apo A-I forms complexes with phospholipids and cholesterol at the plasma membrane in a process that is promoted by ABCA1 activity. There is abundant evidence that ABCA1-mediated cholesterol efflux to apo A-I can occur at the plasma membrane<sup>[51-53]</sup>. It has been shown that optimal cholesterol efflux in macrophages requires binding of the C-terminal domain of apo A-I to a cell-surface-binding site, and the subsequent translocation of intracellular cholesterol to an efflux-competent pool<sup>[54]</sup>. By studying the binding of wild-type and mutant forms of human apo A-I to mouse J774 macrophages, it has been shown that ABCA1 activity creates two types of high affinity apo A-I binding sites at the cell surface. Only 10% of cell-surface-bound apo A-I interacts directly with ABCA1, whereas the rest is bound to lipid domains *via* the C-terminal domain. The low capacity site formed by direct apo A-I/ABCA1 interaction functions in a regulatory role, whereas the much higher capacity site generated by apo A-I/lipid interactions functions in lipidation<sup>[55]</sup>. Vedhachalam *et al*<sup>[53]</sup> have proposed an apo A-I/ABCA1 reaction scheme that involves three steps. First, there is binding of a small regulatory pool of apo A-I to ABCA1, thereby enhancing net phospholipid translocation to the plasma membrane exofacial leaflet; this leads to unequal lateral packing densities in the two leaflets of the phospholipid bilayer. Second, the resultant membrane strain is relieved by bending and by creation of exovesiculated lipid domains. The formation of highly curved membrane surface promotes high affinity binding of apo A-I to these domains. Third, this pool of bound apo A-I spontaneously solubilizes the exovesiculated domain to create discoidal nascent HDL particles. These particles contain 2-4 molecules of apo A-I and a complement of membrane phospholipid classes, together with some cholesterol. A key feature of this mechanism is that membrane bending induced by ABCA1 lipid translocase activity creates the conditions required for nascent HDL assembly by apo A-I. Overall, this mechanism is consistent with the known properties of ABCA1 and apo A-I and reconciles many of the apparently discrepant findings in the literature. Recently, it has been shown that sera with similar HDL cholesterol levels or apo A-I levels differ in

their ability to promote macrophage efflux due to the differences in the concentration of pre- $\beta$  HDL<sup>[56]</sup>.

**ABCG1 and ABCG4:** ABCA1 activity is needed for the predominant pathway for cholesterol efflux to apo A-I and the formation of pre- $\beta$  HDL. However, it is doubtful whether ABCA1 operates alone in the formation of mature  $\alpha$ -HDL. For example, HEK293 cells with ABCA1 overexpression, but without expression of HDL modifying factors like LCAT, PLTP, ABCG1, scavenger receptor class B type 1 (SR-BI), or apolipoprotein M, form pre- $\beta$  HDL, but not  $\alpha$ -HDL. In addition, it appears that the pre- $\beta$  HDL that is formed is a poor substrate for subsequent lipidation by ABCA1, and presumably requires additional non-ABCA1-mediated lipidation for further maturation<sup>[57]</sup>. ABCG1 and ABCG4 or their heterodimers<sup>[58]</sup> might be good candidates for lipidation and maturation of HDL. Synergistic relationships between ABCA1 and ABCG1 and ABCG1/ABCG4 heterodimers have been demonstrated *in vitro*<sup>[59,60]</sup>. Wang *et al*<sup>[61]</sup> have shown that ABCG1 and ABCG4 mediate isotopic and net mass efflux of cellular cholesterol to HDL but not to lipid-poor apo A-I. In addition, mice with a targeted disruption of *Abcg1* display impaired cholesterol efflux to mature HDL<sup>[62]</sup>. The exact mechanism behind ABCG1- and ABCG4-mediated cholesterol efflux is still a matter of debate.

**SR-BI:** SR-BI was identified as an HDL receptor (HDLR) in 1996. SR-BI is primarily expressed in liver and nonplacental steroidogenic tissues, and binds HDL with high affinity. The classic function of SR-BI is to mediate the selective uptake of HDL cholesterol by cells by a mechanism distinct from the classic LDL receptor (LDLR) pathway<sup>[63]</sup>. LDLR mediates endocytosis of the intact LDL particles *via* coated pits and vesicles, and their subsequent hydrolysis in lysosomes<sup>[64]</sup>. SR-BI mediates the selective uptake of HDL cholesterol by cells; primarily in the form of cholesteryl esters. This process involves the transfer of the cholesteryl esters from the hydrophobic core of the HDL particle to the cell, without transfer of the apolipoprotein at the surface of the particle. SR-BI-mediated selective lipid uptake appears to be a two-step process, in which high-affinity lipoprotein binding is followed by receptor-mediated transfer of lipids from the lipoprotein particle to the cell membrane. After lipid transfer, the lipid-depleted lipoprotein particle is released from the cells and re-enters the extracellular space<sup>[65]</sup>. SR-BI also mediates the bidirectional flux of unesterified cholesterol and phospholipids between HDL and cells<sup>[66]</sup>.

Studies in genetically modified mice have revealed that SR-BI in the liver is particularly essential for RCT. In SR-BI<sup>-/-</sup> mice, plasma total cholesterol is elevated approximately twofold, and most of it circulates in abnormally large, heterogeneous, apolipoprotein-E-enriched HDL-like particles<sup>[67]</sup>. In addition, these mice exhibit impaired biliary cholesterol secretion, without concomitant changes in either biliary bile acid or phospholipid secretion<sup>[68]</sup>. Conversely, hepatic overexpression of SR-BI in mice re-

sults in the virtual disappearance of plasma HDL and a substantial increase in biliary cholesterol<sup>[69]</sup>.

**ABCG5 and ABCG8:** At the beginning of the 21st century, two groups almost simultaneously identified mutations in genes ABCG5 and ABCG8, which underlie the disease sitosterolemia<sup>[70,71]</sup>. Sitosterolemia patients accumulate large amounts of plant sterols and exhibit complete abrogation of biliary plant sterol secretion. They also display increased cholesterol absorption and decreased biliary cholesterol secretion<sup>[72,73]</sup>. We now know that half-transporters ABCG5 and ABCG8 function as a heterodimer<sup>[70]</sup> in order to facilitate hepatobiliary cholesterol transport. Double knockout mice for *Abcg5* and *Abcg8* display extremely low biliary cholesterol concentrations in comparison to wild-type animals<sup>[74]</sup>. Overexpression of the human ABCG5 and ABCG8 in mice<sup>[75]</sup> and pharmacological induction of endogenous *Abcg5* and *Abcg8*<sup>[76,77]</sup> both result in increased biliary cholesterol levels. Mice that lack either *Abcg5*<sup>[78]</sup>, *Abcg8*<sup>[79]</sup>, or both<sup>[74]</sup> do not show the same phenotype regarding physiology, which leaves room for discussion about the way these transporters function. Currently, two hypotheses exist. One argues that ABCG5/G8 act as a “flippase”. In this case, the heterodimer shuttles cholesterol from the inner leaflet of the canalicular membrane through a chamber formed by the two half-transporters. This is followed by ATP binding and hydrolysis, which results in a conformational change of the complex. Cholesterol is thereby flipped into the outer membrane leaflet in a configuration that favors its release. Then, cholesterol is ready to be picked up by acceptors<sup>[80]</sup>. The other hypothesis argues that ABCG5/G8 act as a “liftase”<sup>[81]</sup>. In this case, the heterodimer promotes an activated state of cholesterol so that acceptors can easily pick up cholesterol. ABCG5/G8 could form a channel that binds cholesterol. Thereafter, the heterodimer might push cholesterol partly into the lumen when ATP is hydrolyzed (activation of cholesterol). Once cholesterol is activated, mixed micelles and PC vesicles are able to serve as an acceptor for cholesterol.

## Summary

In summary, the classical view describes RCT as follows: the transport of cholesterol from the periphery to apo A-I and HDL by processes that are mediated by ABCA1, ABCG1 and/or ABCG4. The subsequent uptake of HDL cholesterol by the liver involves SR-BI. Thereafter, hepatobiliary cholesterol secretion is mediated by ABCG5/G8 and final excretion is *via* the feces.

## NEW INSIGHTS

How solid is the classical definition of RCT? In recent years, new insights into RCT have been provided, which brings into question the current concept of RCT.

### Classical route

Studies that try to pinpoint the rate-controlling step in RCT



often give rise to confusion. For example, Jolley *et al*<sup>[82]</sup> and Osono *et al*<sup>[83]</sup> has studied the importance of HDL in rate-control of RCT. They have used transgenic mice that expressed variable amounts of simian CETP in order to vary HDL levels. It appears that, in mice, neither the concentration of HDL cholesterol or apo A-I, nor the level of CETP activity dictate the magnitude of RCT<sup>[83]</sup>. Apo A-I<sup>-/-</sup> mice have very low HDL levels. When HDL is rate-controlling for RCT, then RCT should be hampered in apo A-I<sup>-/-</sup> mice. Nevertheless, Jolley *et al*<sup>[82]</sup> have demonstrated that the magnitude of the cholesterol flux from peripheral organs to the liver is virtually identical in mice that lacking apo A-I compared with control animals. They have suggested that the magnitude of RCT is probably ascribed to processes in peripheral organs. Although ABCA1 mediates cholesterol efflux from the periphery, it appears that Abca1<sup>-/-</sup> mice have unaltered hepatobiliary cholesterol secretion and fecal cholesterol excretion, while having virtually absent HDL levels<sup>[84]</sup>. Also, the proposed key player in the liver in HDL uptake, SR-BI, does not control RCT in mice<sup>[85]</sup>. Moreover, the exclusiveness of SR-BI as the sole high-affinity HDLR in the liver was compromised when Martinez *et al*<sup>[86]</sup> identified ecto-F1-ATPase as a high-affinity HDLR in hepatocytes. Furthermore, deficiency of Abcg5 and/or Abcg8 leads to mild<sup>[74,77]</sup> or no<sup>[78]</sup> decrease in fecal neutral sterol secretion in mice. This also questions the rate-controlling properties of these transporters on the magnitude of RCT. In addition, it has been shown that Abcg5/g8-independent, inducible routes exist that can significantly contribute to total hepatobiliary cholesterol output in mice<sup>[87]</sup>. Although most of the above-mentioned studies have been performed in mice and not in humans, it emphasizes the complexity of the mechanisms that underlie RCT.

### Alternative route

In the classical concept of RCT, the liver plays a major role. When hepatobiliary cholesterol secretion is the primary route of cholesterol elimination, inhibition of ABCG5/G8, and hence, diminished hepatobiliary cholesterol secretion, should result in a drastic lowering of fecal neutral sterol excretion. Abcg5/Abcg8 double knockout mice do not show the expected low levels of fecal neutral sterol excretion<sup>[74]</sup>. In addition, Abcb4<sup>-/-</sup> mice, which also have almost no biliary cholesterol secretion, have the same fecal neutral sterol output as their wild-type littermates<sup>[88]</sup>. In addition, Kruit *et al*<sup>[88]</sup> have shown that, in these mice, intravenous radiolabeled cholesterol could be recovered in the feces. These findings indicate that hepatobiliary cholesterol secretion might not be the only route of cholesterol excretion. In mouse models with disturbed biliary secretion, there must be a direct transintestinal pathway for cholesterol excretion. In 2006, van der Velde *et al*<sup>[89]</sup> described significant direct intestinal cholesterol secretion in normal mice. This was later supported by van der Veen *et al*<sup>[90]</sup> who have measured cholesterol fluxes in mice. This route is nowadays referred to as transintestinal cholesterol efflux (TICE; see<sup>[91]</sup> for review) and continues to be elucidated<sup>[92-94]</sup>. Although quantitative cholesterol flux studies

are warranted to quantify exactly the magnitude of TICE in humans, significant secretion of intestinal cholesterol in humans has been observed by Simmonds *et al*<sup>[21]</sup>.

## CONCLUSION

Although medical textbooks have taught us the classical view of RCT for several decades, it is desirable to open our eyes to the new insights into cholesterol excretion. Research on RCT has taken off in recent years. These new insights show us that the classical route for cholesterol excretion cannot be a strictly defined pathway. In addition, an alternative route for cholesterol disposal has come to light in the form of TICE (Figure 1). The new insights into RCT should make us question whether the classical view needs revision.

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