Reverse Cholesterol Transport Revisited
Contribution of Biliary Versus Intestinal Cholesterol Excretion

Gemma Brufau, Albert K. Groen, Folkert Kuipers

Abstract—Reverse cholesterol transport (RCT) is usually defined as high-density lipoprotein–mediated transport of excess cholesterol from peripheral tissues, including cholesterol-laden macrophages in vessel walls, to the liver. From the liver, cholesterol can then be removed from the body via secretion into the bile for eventual disposal via the feces. According to this paradigm, high plasma high-density lipoprotein levels accelerate RCT and hence are atheroprotective. New insights in individual steps of the RCT pathway, in part derived from innovative mouse models, indicate that the classical concept of RCT may require modification. (Arterioscler Thromb Vasc Biol. 2011;31:1726-1733.)

Key Words: ABC transporter ■ atherosclerosis ■ genetically altered mice ■ lipoproteins ■ macrophages

Lipid accumulation in macrophages, leading to formation of foam cells, is a critical initial event in atherosclerosis development. The major lipid species stored in foam cells is cholesterol, either in its free form or esterified to a fatty acid. An imbalance of cholesterol uptake, synthesis, and export by macrophages underlies the development of foam cells. Currently, the main strategies to interfere with cholesterol accumulation in macrophages are still focused on reduction of the amount of “substrate,” ie, the concentration of atherogenic lipoproteins in plasma. Inhibition of cholesterol synthesis by statins, leading to lowering of low-density lipoprotein (LDL) cholesterol in plasma, is a successful approach to limit cholesterol uptake by the macrophages and progression of plaque formation. However, intensive statin treatment reduces the incidence of cardiovascular events only by ≈25%. It is generally assumed that in most of the remaining 75% of cases, atherosclerosis is already too far advanced to allow successful prevention of cardiovascular incidents. Consequently, the pathways involved in export of excess cholesterol from foam cells and its removal from the body are currently under intense investigation to provide novel targets for antiatherosclerotic therapies. The net result of these pathways is usually referred to as reverse cholesterol transport (RCT), a term coined by Glomset more than 4 decades ago.

In the literature, RCT is usually defined as the process by which excess cholesterol from cells in peripheral tissues and organs, including macrophages in vessel walls, is transported to the liver for removal from the body through excretion as neutral sterols or bile acids via the bile into the feces. High-density lipoprotein (HDL) is generally believed to protect against atherosclerosis by acting as the specific cholesterol carrier in the RCT pathway by delivering its cholesterol cargo to the liver. The term centripetal cholesterol flux has been introduced to describe bulk cholesterol transfer from periphery to the liver, with the inherent assumption that the magnitude of this flux by some means determines hepatobiliary removal of cholesterol. From a functional point of view, it would be instrumental to define relevant RCT as the flux of excess cholesterol from the peripheral tissues (including macrophages) into feces independent of its route. Methods have been developed to quantify the macrophage to feces flux of cholesterol, but these have been applied only in rodents.

Recently, several studies have provided evidence for alternative routes for removal of (excess) cholesterol that does not involve HDL or the hepatobiliary route. Here, we review the most relevant new findings that may constitute a basis for a new definition of RCT.

HDL
HDL is generally considered to represent the primary mediator of RCT. However, HDL by no means refers to a homogenous class of lipoproteins. Up to 10 subpopulations of HDL can be classified depending on 5 physicochemical properties: (1) shape (discoidal or spherical), (2) density (HDL₂ being the less dense and HDL₃ the most dense), (3) size (the diameter may range from 7.6 to 10.6 nm), (4) protein composition (HDL containing both apolipoprotein [apo] A-I...
and apoA-II or only apoA-I), and (5) surface charge.17 Probably, the number of HDL subspecies present in vivo is even larger because proteomic analyses have indicated that human HDL can contain up to \( \approx 100 \) different proteins.18–21 For many of these proteins the number of molecules present in plasma is smaller than the number of HDL particles, implying that not all particles have the same protein cargo. In addition, the space for proteins on an HDL particle is limited because of its relatively small size.

In apoA-I-synthesizing organs, such as the liver and the intestine,22 discoidal HDL (also known as pre-\( \beta \) HDL) is produced23 and subsequently lipitated with free cholesterol and phospholipids from peripheral cells (including macrophages) to form larger, more mature HDL\(_2\) particles. ApoA-I is also associated with small and large chylomicros produced in the intestine,24 from which it can be transferred to HDL.25,26

ApoA-I is able to activate lecithin:cholesterol acyltransferase (LCAT), which in turn esterifies free cholesterol molecules present at discoidal HDL. This process will result in the transition from discoidal HDL to mature spherical HDL\(_2\) (for review, see Dobiasova and Frohlich27). Several attempts have been made to elucidate the role of LCAT in RCT, because this enzyme plays a crucial role in determining plasma HDL levels (for review, see Cabaresi and Franschini28). Glomset was the first to point to LCAT activity as first and potentially rate-limiting step in RCT. According to this author, LCAT activity maintains a gradient of free cholesterol between cell membranes and extracellular acceptors, such as HDL.29 However, recent data indicate that LCAT is not required for the flux of cholesterol from the macrophages to the liver.29–31

Nascent HDL particles interact with the ATP-binding cassette transporter A1 (ABCA1), a membrane-associated protein that is ubiquitously expressed in peripheral tissues and macrophages, as well as in liver and intestine.23 The importance of ABCA1 in HDL formation is evident from the phenotype of patients with Tangier disease, an autosomal recessive disorder characterized by 2 nonfunctional ABCA1 alleles and extremely low levels of HDL.32–34 In vitro experiments on cultured cells have provided evidence that in addition to ABCA1, ABCG1 may be involved in the HDL lipidation process.8 The cellular cholesterol and phospholipid transfer mediated by this transporter is donated to more mature HDL rather than to pre-\( \beta \) HDL.35 It should be noted that in vivo evidence for a dominant role of this transporter is lacking: Abcg1 knockout mice show no evident (plasma) lipid phenotype when kept on chow diet.36 However, Abca1/Abcg1 double knockout mice do show a very severe phenotype with massive lipid accumulation in several tissues including lung and liver.37 Apparently, in the absence of Abcg1, Abca1 compensates for the lack of efflux capacity in most organs. A very recent article demonstrates that these transporters have functions beyond control of lipid efflux from cells:38 their concerted action appears to be pivotal for control of hematopoietic stem cell proliferation.

Cholesterol delivery to the liver, as well as to other (cholesterol-requiring) organs, can be mediated through various pathways. In this respect, it is important to distinguish between the flux of free cholesterol and that of cholesterol ester. In all classes of lipoproteins, cholesterol is predominantly carried in its esterified form. This is probably the reason why most published studies primarily address transport of cholesterol ester into target organs. However, some important early studies have shown that the flux of free cholesterol is at least 1 order of magnitude larger than the flux of esterified cholesterol and that the mechanism by which transport proteins mediate these fluxes may be quite different.30,39 In rodents, in which HDL is the prominent lipoprotein class, the main route for both free cholesterol and cholesteryl ester uptake by the liver is assumed to involve selective uptake on direct interaction between HDL and the scavenger receptor BI (SR-BI/SCARB1).40 However, holoparticle uptake has also been described: an interesting novel route is mediated by a complex of different proteins, including F1F0-ATPase and the nucleotide receptor purinergic receptor P2Y, G-protein coupled 13.41–43 The relative contribution of the different pathways to total cholesterol uptake has never been determined.42 The routing of HDL cholesterol uptake is even more complex in animal species that express cholesteryl ester transfer protein. Cholesteryl ester transfer protein mediates transfer of cholesteryl esters from HDL to LDL and very-low-density lipoprotein. Hepatic uptake of HDL-derived cholesterol is in this case also mediated by the LDL receptor. In 2004, Schwartz et al40 reported on the basis of isotope exchange studies that basically all hepatic cholesterol ester uptake follows the LDL receptor route in humans. Unfortunately, this result has never been confirmed, and it should be stressed that this assumption only holds for cholesteryl ester uptake, which, also according to Schwartz et al.,40 is one-tenth of that of free cholesterol transport. Recently, direct evidence for a role of SR-BI in human HDL metabolism has been obtained in a study with subjects carrying the Pro297Ser mutation in SR-BI.44 These subjects, heterozygous for the mutation in SR-BI, showed a 50% increase in plasma HDL. Experiments in mice in which SR-BI with this mutation was expressed on a SR-BI-null background showed dysfunctional uptake of HDL.45 Hence, even a heterozygous mutation in SR-BI apparently causes a clear phenotype in humans, suggesting that this protein is much more important than has been assumed thus far.

**RCT: Involvement of HDL**

Although the role of HDL in RCT is generally considered to explain the antiatherogenic properties of this lipoprotein, there is in fact very little evidence that this lipoprotein actually regulates the rate of RCT in vivo. Most of the initial supportive evidence for the existence of the classical RCT pathway was derived from in vitro studies initiated by a landmark study by Fielding and Fielding demonstrating uptake of HDL cholesterol by cells.36 However, there is increasing evidence that the antiatherogenic properties of HDL do not depend on the total amount of this lipoprotein in blood but rather on the presence of specific HDL subpopulations.47

Recent studies have confirmed the contributions of macrophage ABCA1 and ABCG1 to the RCT pathway in mice, using an ex vivo macrophage labeling procedure.48–50 Adorni
et al attempted to quantify the contribution of the different transporters to total cellular cholesterol efflux.53 Using knockdown approaches or specific inhibitors, the activity of ABCA1, ABCG1, and SR-BI was selectively abrogated in cultured macrophages. About 30% of total cholesterol efflux could not be accounted for by either of the transporters and was considered to be due to aqueous diffusion of cholesterol. The underlying molecular mechanism of ABCA1- and ABCG1-mediated lipid efflux is a matter of controversy that has been the subject of a number of recent reviews54,55 and will therefore not be covered here. A series of intriguing results was recently published by Cuchel et al.53 These authors infused apo-A-I phospholipid complexes (also denoted as reconstituted HDL [rHDL]) into wild-type, Abca1-, Abcg1- and Sr-bi-deficient mice. Large amounts of free cholesterol were mobilized by rHDL in all genotypes except the Sr-bi\(^{-/-}\) mice, suggesting that this protein plays an important role in a specific type of cholesterol efflux into plasma; it is tempting to speculate that this cholesterol may originate from the liver.

In addition to apoA-I and HDL, many other apolipoproteins are also able to mediate cholesterol efflux in vitro.54 Thus, apoE-containing very-low-density lipoprotein and LDL are also able to pick up cholesterol from cells and could hence theoretically contribute to RCT. The question whether the plasma HDL concentration correlates with the rate of RCT, defined as the flux of peripheral cholesterol into feces, independently of its route, has been addressed in a number of recent studies. Importantly, in several animal models of (partial) HDL deficiency, no (positive) correlation could be found.4–6,29,55–57 Modulation of apoA-I, LCAT, and SR-BI activity in mice resulted in marked changes in HDL cholesterol levels without any effect on biliary cholesterol secretion or fecal sterol excretion.57 In line with this, the complete absence of HDL in Abca1\(^{-/-}\) mice also did not affect biliary or fecal cholesterol excretion.55,56 Infusion of reconstituted rHDL into HDL-deficient apoA-I\(^{-/-}\) mice did not increase fecal sterol excretion.57 LCAT heterozygous mice display a severe plasma HDL reduction whereas macrophage to feces RCT is fully preserved.28 Elegant studies by Dietschy’s group have demonstrated that the concentration of circulating HDL plays no role in the mass transport of cholesterol from the peripheral organs to the liver in mouse models.4–6

Data on the relationships between HDL levels and fecal sterol excretion in humans are scarce and ambiguous. Miettinen et al showed, surprisingly, a negative correlation between plasma HDL cholesterol levels and fecal neutral sterol excretion in a large study comprising 63 male normolipidemic subjects.58 Furthermore, doubling HDL cholesterol levels through cholesteryl ester transfer protein inhibition by torcetrapib had no effect on fecal sterol excretion in 16 individuals.59 Similarly, 2 very small studies, one with only 2 patients with low HDL cholesterol due to LCAT deficiency and one with 2 patients with familial combined hyperlipidemia, failed to show a difference in neutral sterol excretion compared with controls.60,61 In contrast, in 12 patients with familial hyperalphalipoproteinemia, plasma HDL cholesterol levels did correlate with fecal sterol excretion,62 and 2 intervention studies showed a clear increase in fecal sterol excretion after infusion of pro-apoA-I or rHDL in 4 and 16 individuals, respectively63,64 Altogether, a relationship between plasma HDL cholesterol concentrations and fecal sterol excretion in humans and animal models is by no means evident. However, in these studies, only the plasma concentrations of HDL cholesterol were determined, whereas the functionality of the HDL particles present may be more relevant with respect to RCT.

Changes in HDL protein and lipid composition have been associated with loss of HDL functionality.55 For instance, HDL isolated from transgenic mice overexpressing apoA-II or phospholipid transfer protein (which transfers phospholipids between HDL and very-low-density lipoprotein) show reduced functionality in cholesterol efflux assays.56,65 Treatment of HDL with 15-lipoxygenase (an enzyme involved in formation of lipid peroxides) also reduced HDL cholesterol acceptor activity.68,69 In addition, changes in HDL due to infection, inflammation, or diabetes may also result in loss of its functionality, or, adversely, it has been reported that HDL may even become proinflammatory.70–73 For example, impaired cholesterol efflux toward HDL isolated from patients with acute sepsis or from mice injected with lipopolysaccharide has been reported.70

### The Intestine and RCT

A general problem with the interpretation of available data, for instance those generated by Dietschy’s group, is caused by the hepatobiliary paradigm, which states that all centripetal cholesterol flux originating from the periphery by definition enters the liver. We and others have recently falsified this paradigm in a series of studies (Table). These studies demonstrate the presence of a nonbiliary route for fecal sterols and imply the presence of a pathway for plasma cholesterol via enterocytes into the intestinal lumen. In principle, cholesterol present in the intestinal lumen can originate from enterocytes either as a component of shed cells or on secretion of locally synthesized cholesterol. Alternatively, plasma-derived cholesterol can be transported directly through the intestinal wall by a pathway called transintestinal cholesterol excretion (TICE), which has not yet been fully defined in molecular terms (for review, see73) (Figure). It has been estimated that the contribution of cell shedding adds, at most, \(\approx 20\%\) of fecal neutral sterols in mice.9,10,76 Furthermore, the contribution of intestine-derived de novo synthesized cholesterol to fecal neutral sterols is small in mice.10 Therefore, it is likely that most of the cholesterol excreted as neutral sterols originates from nonabsorbed dietary cholesterol, biliary cholesterol, or TICE. Recent work, outlined below, has demonstrated that TICE is a quantitatively important process.

Although most of the studies have been carried out in mouse models, there is evidence for the existence of TICE in humans as well. As early as the late 1960s, Simmonds et al unintentionally quantified part of TICE in humans by perfusing the upper jejunum with a solution of bile salts, triglycerides, and radiolabeled cholesterol. This study estimated that \(\sim 44\%\) of total fecal sterol output must originate from endogenous (ie, nonhepatobiliary) sources. In addition, patients with biliary obstruction still excrete substantial amounts of neutral sterol into feces.78,79 It seems almost
obvious that during evolution, efficient bypass pathways for cholesterol to leave the body have developed, in particular when considering the substantial (net) centripetal cholesterol flux. This flux has been estimated to amount to up to \( \approx 15 \) mg/kg per day in humans, which is almost equal to the published values for fecal sterol output.\(^{80}\) In rodents, the relative magnitude of these fluxes is \( \approx 5\)-fold higher than in humans, and the existence of alternative pathways for whole body cholesterol export has now been firmly established.\(^ {80}\) As early as the 1920s, Sperry reported that bile diversion in mice does not decrease fecal neutral excretion, suggesting an additional pathway of cholesterol excretion.\(^ {81}\) Kruit et al found a reduction of TICE in mice deficient for this transporter using their in vivo approach.\(^ {9}\) At present it is not possible to mice. More recently, van der Veen et al developed an intestinal perfusion method applicable to mice. More recently, van der Veen et al developed an in vivo method to estimate TICE.\(^ {10}\) Using 3 different stable isotopes, these authors were able to quantify all major cholesterol fluxes toward feces in mice. \textit{Grosso modo}, the results obtained with this methodology were similar to those of van der Velde et al.\(^ {9}\) However, there was also an important difference. Using their intestinal perfusion methodology, van der Velde et al were unable to demonstrate a role for the dimeric cholesterol transporter Abcg5/Abcg8 in mice. \textit{Abcg8}\(^ {−/−}\) mice showed, in fact, an unaltered rate of TICE compared with wild-type controls. In contrast, van der Veen et al found a reduction of TICE in mice deficient for this transporter using their in vivo approach.\(^ {10}\) At present it is not clear whether and why the Abcg5/Abcg8 heterodimer loses its activity in the intestinal perfusion setup. Collectively, at least for mice, there is now overwhelming evidence for the existence of alternative pathways, in addition to the hepatobiliary route, to remove cholesterol from the body. However, limited data are available on the source of cholesterol excreted via TICE and the lipoprotein(s) involved in delivering cholesterol to this pathway.

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**Table.** Studies in Which Biliary Cholesterol Does Not Account for Fecal Cholesterol Excretion

<table>
<thead>
<tr>
<th>Animal Model</th>
<th>Cholesterol in Bile</th>
<th>Neutral Sterol Excretion</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mdr2(^ {−/−}) vs wild-types</td>
<td>6- to 19-fold decreased*</td>
<td>Not changed or slightly increased</td>
<td>9,11</td>
</tr>
<tr>
<td>Abcg8(^ {−/−}) vs C57Bl6</td>
<td>2.5-fold decreased*</td>
<td>Unchanged</td>
<td>9</td>
</tr>
<tr>
<td>ABCG5/G8(^ {−/−}) vs controls</td>
<td>(-7)-fold decreased†</td>
<td>Unchanged</td>
<td>91,92</td>
</tr>
<tr>
<td>Abcg5(^ {−/−}) vs controls</td>
<td>(-3)-fold decreased†</td>
<td>Unchanged</td>
<td>93</td>
</tr>
<tr>
<td>ACAT2 ASO vs control</td>
<td>Unchanged†‡</td>
<td>2.1-fold increased</td>
<td>14</td>
</tr>
<tr>
<td>ACAT2(^ {−/−}) vs control</td>
<td>Unchanged†‡</td>
<td>2.1-fold increased</td>
<td>14</td>
</tr>
<tr>
<td>Abca1(^ {−/−}) vs control</td>
<td>Unchanged*†‡</td>
<td>Not changed or slightly increased</td>
<td>4,5,56</td>
</tr>
<tr>
<td>NPC1L1(^ {−/−}) vs control</td>
<td>(-4)- to 20-fold decreased†</td>
<td>Unchanged</td>
<td>16,65</td>
</tr>
<tr>
<td>NPC1L1(^ {−/−}) vs controls</td>
<td>Unchanged†</td>
<td>7.3-fold increased</td>
<td>91</td>
</tr>
<tr>
<td>GW3965 vs control diet (in \textit{Mdr2}(^ {−/−}))</td>
<td>Unchanged*</td>
<td>2.1-fold increased</td>
<td>11</td>
</tr>
<tr>
<td>Cyp7A1(^ {−/−}) vs Cyp7A1(^ {+/+})</td>
<td>Unchanged†‡</td>
<td>2.3-fold increased</td>
<td>13</td>
</tr>
<tr>
<td>Bile-diverted rat</td>
<td>No biliary cholesterol entering the intestine</td>
<td>2.2-fold increased</td>
<td>94</td>
</tr>
</tbody>
</table>

*Changes observed in biliary cholesterol secretion.† Changes observed in biliary cholesterol secretion.‡ Changes observed in biliary cholesterol secretion.
Apart from Abcg5/Abcg8, no other enzymes/transporters have so far been identified that participate in the process. To identify potential candidates involved in TICE, expression of genes encoding proteins involved in cholesterol trafficking has been studied in the intestines of mice that exhibit an increased TICE flux. Based on gene expression analyses, no involvement of Npc1l1, Mttp, Lrp, Ldlr, Vldlr, Abca1, or Abcg1 in this pathway could be established.9,12,82

In Vivo RCT Measurement
Several methodologies have been developed to “measure” RCT in vivo. Considering the fact that the actual amount of cholesterol derived from macrophages can theoretically constitute only a minor percentage of fecal sterol excretion, the need for a macrophage-specific RCT measurement is evident. Probably the most extensively used method is the one developed by Rader and colleagues.7,83 In this method, macrophage cell lines or primary macrophages isolated from donor mice are labeled with [3H]cholesterol by ex vivo loading with radiolabeled acetylated LDL. Subsequently, these macrophages are injected into the peritoneal cavity of acceptor mice, and the appearance of cholesterol radioactivity in macrophages are injected into the peritoneal cavity of acceptor mice, and the appearance of cholesterol radioactivity is followed over time in plasma, liver, bile, and feces.7 This method has been successfully applied in a number of studies, including those aimed at estimating the contribution of Abca1, Abcg1, and Sr-b1 to macrophage RCT.53,84

Although this assay clearly demonstrates a flow of labeled cholesterol from injected macrophages to the plasma compartment and ultimately into feces, one wonders to what extent this flux mirrors the actual efflux of cholesterol from macrophages/foam cells localized in atherosclerotic plaques. This certainly holds true for the original protocol in which the J774 “macrophage” cell line was used.49 Clearly, the functionality of these cells differs from that of primary murine macrophages. Interestingly, to the best of our knowledge, the outcome of this assay has never been compared with that of an experiment in which cholesterol was injected directly into the peritoneal cavity, for instance encapsulated in triglyceride-rich particles. A limitation of the assay is the fact that macrophage RCT is calculated on the basis of radioactivity (ie, counts) measured in plasma, bile, and feces, without correction for the specific activity of cholesterol in these compartments. When mouse models are compared with identical amounts of cholesterol in the different compartments, this obviously does not interfere with interpretation of the results. However, when plasma levels of cholesterol, for instance, are widely different, comparison is by nature at best qualitative. Therefore, results obtained with this method can easily underestimate or overestimate the actual rate of RCT. Taking these limitations into account, the ability to follow the fate of macrophage-derived cholesterol has evidently produced very interesting results. A case in point is the recent study of Temel et al.85 This work investigated whether macrophage-derived cholesterol could be excreted via TICE. Mice with acute biliary diversion were injected intraperitoneally with cholesterol-loaded macrophages, and the released radiolabeled cholesterol appeared in the intestinal lumen at unaltered rates compared with sham-operated control mice. Clearly, this result does not prove that mice dispose of their macrophage-derived cholesterol predominantly via TICE. It does demonstrate, however, the redundancy of the hepatobiliary pathway for cholesterol excretion in mice.

Several other attempts have been made to measure RCT in vivo. As mentioned, Dietschy’s group developed a method to quantify the rate of centripetal cholesterol flux by adding up the rates of cholesterol synthesis and LDL cholesterol uptake in the extrahepatic tissues.4–7,67 However, a limitation of this method is that it inherently implies that the entire centripetal cholesterol flux originating from the periphery by definition enters the liver. Stein et al developed a method to measure quantitatively the removal of a localized cholesterol deposit and defined radiolabeled cholesterol deposit in rodents.86 These authors injected cationized LDL, labeled with trace amounts of [3H]free cholesterol into the rectus femoris muscle of mice and rats. According to these authors, this model system may simulate conditions occurring in the arterial wall during atherosclerosis because this modified lipoprotein adheres to the extracellular matrix, inducing the influx of mononuclear cells. However, whether this is actually the case has not yet been proven. Hellerstein and colleagues developed, from the early 1990s onwards, several kinetic models to quantify fluxes of biologically active molecules in vivo to predict their flow through complex pathways. These authors have been successful in measuring cholesterol synthesis and turnover and lipogenesis, among others (for review see87,88). A model able to predict the flux of cholesterol from the peripheral tissues to the feces has as yet been published only in abstract form.89,90

Conclusions and Perspectives
Glimset3 proposed the RCT concept more than 4 decades ago. Because it provided a very plausible explanation for a route via which cholesterol might leave the body, this concept became a generally accepted paradigm. Until recently, the validity of the paradigm had never been rigorously tested. However, we now know that transport via HDL and removal through the hepatobiliary secretion is certainly not the only pathway for excretion of “excess” cholesterol. Mice and humans without measurable HDL still excrete neutral sterols, and abrogation of biliary cholesterol secretion, at least in mice, does not influence the fate of fecal sterol excretion. We conclude that in addition to the HDL-mediated hepatobiliary pathway, there are alternative routes for cholesterol excretion. The distribution of the total flux across the different pathways has as yet been determined only in mouse models and may in fact vary under different conditions in mice and humans. However, we have shown that the direct TICE pathway is an important route for excretion of cholesterol, at least in mice. This pathway is amenable to upregulation by both dietary and pharmacological means, making it a very attractive target for development of novel therapeutical modalities to enhance body cholesterol turnover and thereby reduce cardiovascular risk.

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Disclosures
None.

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