Role the TICE?
Advancing the Concept of Transintestinal Cholesterol Excretion

Uwe J.F. Tietge, Albert K. Groen

Cholesterol accumulation in the body is associated with disease, most prominently atherosclerosis.1 Cholesterol is either taken up from the diet or de novo synthesized in almost all body cells.2 It is essentially a metabolically inert molecule, the sterol nucleus cannot be degraded, and the only way to remove substantial amounts of cholesterol from the body is fecal excretion either directly or after conversion into bile acids.2 Fecal excretion can occur via 2 independent pathways. The first pathway is represented by biliary secretion, which has been extensively characterized and studied.3 The second pathway is cholesterol excretion by enterocytes, a mechanism that has gained considerable attention during the last 5 years. In 2007, the enteral route of cholesterol elimination from the body was coined as transintestinal cholesterol excretion (TICE; Figure).4

Initial studies established a relatively high uptake rate of LDL cholesterol similar to the setup of Le May et al10 failed to demonstrate TICE in vitro. In this system intestinal explants from both mice and humans were mounted, showing activity of the pathway for the first time in humans.10 Le May et al10 show that low-density lipoprotein (LDL) as well as high-density lipoprotein (HDL) is able to serve as a cholesterol source for TICE.10 The observation that TICE is fueled by apolipoprotein B–containing lipoproteins is not too surprising, given previous data obtained in mouse models in which ACAT2 activity has been abolished11 as well as data using infusion of chylomicron-like emulsion particles,2 from which cholesterol is resecreted by the liver within apolipoprotein B–containing lipoproteins. Furthermore, previous kinetic studies established a relatively high uptake rate of LDL cholesterol into the intestine.12 However, the data on HDL are unexpected. Kinetic studies indicated that the whole of the intestine contributes only ≈6% to total HDL cholesterol uptake, whereas >40% is taken up into the liver.13

While the HDL route is also not followed up in the studies by Le May et al,10 their data do indicate a potential involvement of the LDL receptor (LDLR) on the basolateral side, because PCSK9 had no impact on TICE in mice lacking LDLRs.10 However, when TICE was investigated in LDLr knockout mice, a 40% increase, although just below the expected. Kinetic studies indicated that the whole of the intestine contributes only ≈6% to total HDL cholesterol uptake, whereas >40% is taken up into the liver.13 Counterintuitively, on treatment with liver X receptor agonists, that have uniformly been shown to increase TICE, HDL cholesterol uptake into the intestine decreases.13,14 In addition, in vivo studies investigating TICE after injection of HDL particles containing labeled cholesterol similar to the setup of Le May et al10 failed to demonstrate a significant role for this lipoprotein subclass in TICE.9 Additional studies will be required to resolve this issue, ideally using different concentrations of HDL cholesterol, because these were rather high in the current report.10

The work by Le May et al10 in this issue of *ATVB* represents an important technical as well as conceptual advancement of our understanding of TICE. These authors demonstrate in a series of in vitro as well as in vivo studies that TICE depends on presence of oxygen and is drastically lower at 4°C, and hence may qualify as an active metabolic process. Ussing chambers were used to demonstrate TICE in vitro. In this system intestinal explants from both mice and humans were mounted, showing activity of the pathway for the first time in humans.10
Figure. Schematic representation of cholesterol fluxes in enterocytes related to the transintestinal cholesterol excretion (TICE) pathway. The cholesterol pool of the intestinal cell is fueled by uptake from the intestinal lumen via apically localized NPC1L1, endogenous synthesis, and via uptake of cholesterol from high-density lipoprotein (HDL) and apolipoprotein B (apoB)-containing lipoproteins on the basolateral side (blood compartment). Apically, the main contributor to TICE is the ABCG5/G8 heterodimer; ABCB1a/b might also play a role as well as an additional route that has not yet been identified. On the basolateral side, the main cholesterol donor for TICE seems to be apoB-containing lipoproteins in a pathway that seems to involve modulation of low-density lipoprotein receptor (LDLR) expression; HDL might represent a contributing factor. TICE can be increased by liver X receptor (LXR) activation as well as dietary plant sterols, partly dependent on functional ABCG5/G8 expression. In addition, high-fat diet and PPARδ activation stimulate TICE. The role of different intracellular pathways of cholesterol trafficking connecting basolateral uptake and apical secretion is currently unclear.

among a variety of substrates is also capable of translocating cholesterol over the cell membrane. In Abcb1a/b knockout mice, TICE was significantly decreased by 26.5%10 compared with 40% previously observed in Abcg5 knockout mice.3 Although Abcb1a/b seems to contribute, it is also clearly not the long sought switch to turn TICE on or off.

In summary, the interesting work by Le May et al10 clearly represents an important step to increase our understanding of the TICE pathway. However, still more work will be required to delineate the key steps of its regulation, namely the lipid-protein substrates, the cellular receptors, and transporters involved, and the intracellular routes of cholesterol trafficking. However, especially the link of TICE to the LDL pathway is exciting. Given the current problems of the HDL field, a new angle to reduce LDL cholesterol and preferentially excrete this proatherogenic cholesterol from the body bears the potential to have a major impact in the continuing fight against atherosclerotic cardiovascular disease.

Disclosures

None.

References


Kev Words: atherosclerosis ■ cholesterol ■ HDL ■ intestine ■ LDL ■ lipoprotein ■ liver
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