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 estimated TICE to contribute ≥30% to total fecal neutral sterols excreted from the body in wild-type mice,5 which is quite a substantial part. This number is fueling the hope that, if accessible to therapeutic modulation, substantial amounts of cholesterol can be excreted via TICE from the body using drugs that would be predicted to only have minimal systemic side effects, because local action in the gut would seem sufficient. About regulation of TICE, thus far, high-fat diet,6 plant sterols,7 and liver X receptor activation8 as well as PPARb ligands9 have been identified as activators. Although recent work indicated that apolipoprotein B–containing lipoproteins are the likely preferred cholesterol substrate for TICE,9 the basolateral lipoprotein receptors as well as intracellular trafficking pathways involved in TICE have remained elusive. On the apical side, the obligate heterodimer Abcg5/g8 was characterized to be at least an important contributing factor; however, even in a whole body Abcg5 or Abcg8 knockout mouse, TICE is not abolished.3 In addition, previous studies suggested that TICE is an active metabolic process, but formal experimental evidence for such a postulate was lacking.

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

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 rescreted 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 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

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 repressed TICE, whereas statin treatment activated it.10 This opens a viable clinical perspective with a new hypothesis to be tested in translational medicine, because a number of PCSK9 inhibiting treatment modalities are currently evaluated in humans.15 The results on PCSK9 are very consistent, and the authors demonstrate in addition that the PCSK9 effect is fully dependent on functional expression of LDLRs, 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 level of statistical significance, was observed.10 These data represent a conundrum that is very hard to reconcile. It would be interesting to test not only human LDL, but also endogenous LDL from Ldlr knockout mice as TICE substrate in the knockout as well as in the wild-type model to exclude or confirm that specific alterations in the LDL itself change its availability for TICE. In addition, it seems relevant to investigate TICE in heterozygous Ldlr knockouts.

On the apical side, the studies by Le May et al10 suggest a contribution for ABCB1a/b,10 a multidrug transporter that

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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% compared with 40% previously observed in Abcg5 knockout mice. 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 al 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, the potential to have a major impact in the continuing fight 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 connecting basolateral uptake and apical secretion is currently unclear.

**References**

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