Para-bile-osis Establishes a Role for Nonbiliary Macrophage to Feces Reverse Cholesterol Transport

J. Mark Brown, Ryan E. Temel, Gregory A. Graf

Elimination of excess cholesterol by the reverse cholesterol transport (RCT) pathway opposes atherosclerotic cardiovascular disease. RCT begins with the mobilization of excess free cholesterol from macrophage foam cells in the artery wall to high-density lipoproteins. After esterification of cholesterol in the plasma compartment by lecithin cholesterol:acyltransferase, cholesteryl esters can be selectively delivered to the liver via the class B type 1 scavenger receptor. Alternatively, CETP (cholesterol ester transfer protein) may exchange cholesteryl esters for triglycerides on apolipoprotein B–containing lipoproteins, which can deliver cholesterol to hepatocytes by receptor-mediated endocytosis. Cholesterol elimination from the liver requires transport across the canaliculmonary surface by the ABCG5/G8 transporter or the BSEP (bile salt export protein, ABCB11) after cholesterol conversion to primary bile acids. However, a fraction of cholesterol is reabsorbed in the proximal small intestine via NPC1L1 (Niemann-Pick C1-Like 1) and bile acids in the distal small intestine to primary bile acids. Nevertheless, a fraction of cholesterol originating from both the liver and small intestine may exchange cholesteryl esters for triglycerides on apolipoprotein B–containing lipoproteins, which can deliver cholesterol to hepatocytes by receptor-mediated endocytosis. Cholesterol elimination from the liver requires transport across the canaliculmonary surface by the ABCG5/G8 transporter or the BSEP (bile salt export protein, ABCB11) after cholesterol conversion to primary bile acids. However, a fraction of cholesterol is reabsorbed in the proximal small intestine via NPC1L1 (Niemann-Pick C1-Like 1) and bile acids in the distal small intestine to primary bile acids.

The pair was treated with ezetimibe to block the reabsorption of cholesterol secreted by the liver into bile and by the small intestine into the lumen. Rat macrophage foam cells containing radiolabeled cholesterol were then intraperitoneally injected into one of the paired animals. Because the bile of the injected rat was diverted to its partner, the appearance of radiolabeled cholesterol in the feces of the injected rat was used to determine the contribution of TICE to macrophage RCT. The hepatobiliary contribution was determined by measuring radiolabeled sterol in the feces of the biliary diversion recipient rat. Under these conditions, TICE accounted for ≈20% of macrophage RCT.

This creative study clearly establishes TICE as a contributor to macrophage-derived cholesterol elimination in a conscious, preclinical rodent model. However, an important consideration is that the experiment was conducted under the nonphysiological condition of ezetimibe treatment. On one hand, ezetimibe was an essential tool to prevent the noninjected rat from reabsorbing radiolabeled cholesterol and sending it back to its donor via the hepatobiliary pathway. On the other hand, ezetimibe treatment fundamentally alters intestinal cholesterol metabolism resulting in increased cholesterol synthesis and reduced expression of liver X receptor target genes such as Abcg5/g8 and Aboal. In addition, ezetimibe is a pharmacological stimulator of TICE because it blocks the reabsorption of cholesterol originating from both the liver and small intestine.

Another caveat to the study is the absence of a gallbladder in rats and the continual secretion of bile into the intestinal lumen. Although it has been reported that rats, mice, and humans have similar rates of TICE, it will be important to determine the relative contributions of TICE and hepatobiliary cholesterol excretion to macrophage RCT in an parabiosis animal model in which the delivery of gallbladder bile to the intestinal lumen is intermittent and coordinated with food intake.

Although this novel approach reaffirms earlier evidence for both biliary and nonbiliary contributions to macrophage RCT, true quantification remains elusive. Irrespective of the absolute contribution, the critical question that remains is how to therapeutically stimulate RCT to provide benefit to those having atherosclerotic cardiovascular disease. TICE is an attractive pathway given that accelerating hepatobiliary...
cholesterol secretion is expected to promote saturation of gallbladder bile and increase the risk of gallstone formation. Recent studies, again by the Groen group, demonstrate that TICE has a highly dynamic range and impressive capacity to export cholesterol into the feces in mice treated with a farnesoid X receptor agonist. Similarly, recent studies indicate that TICE is active in humans and is stimulated by ezetimibe treatment. Thus, the rodent models not only recapitulate features of TICE in humans but also suggest that TICE is a druggable pathway. Further investigation into the key mediators of TICE and their regulation in the intestine are critical to unlock the therapeutic potential of this antiatherosclerotic pathway.

Disclosures

None.

References


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