commentary

Emerging pathways in the regulation of whole body cholesterol flux: therapeutic opportunities to target atherosclerosis?[1]

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CVD remains one of the most frequent causes of morbidity and mortality globally. Increased awareness of lifestyle factors (nutrition/exercise), as well as the refinement of lipid-lowering therapies, has availed some progress in reducing the incidence of CVD. Historically, the hepatic regulation of lipid and cholesterol homeostasis and its contribution to CVD has been the primary focus of research to target lipid-lowering therapy. However, breakthroughs in the understanding of how the intestine complements the liver in whole-body cholesterol homeostasis have provided new advances in our approach to anti-atherosclerotic targets.

It has emerged that both the liver and intestine are collaboratively involved in the regulation of whole body cholesterol homeostasis. For example, treatment with the drug ezetimibe (inhibitor of Niemann-Pick C1-Like 1 [NPC1L1] protein-mediated cholesterol absorption by the enterocyte), not only reduces intestinal cholesterol absorption, but can simultaneously increase the rate of cholesterol synthesis in humans (1). Conversely, several studies have reported that treatment with HMG-CoA inhibitors can upregulate intestinal cholesterol absorption (2, 3). Collectively, these studies highlight the complementary action of both the liver and the intestine in cholesterol homeostasis (Fig. 1).

In the current issue of the *Journal of Lipid Research*, Dikkers et al. (4) elucidate a role of hepatic deficiency and pharmacological inhibition of microsomal triglyceride transfer protein (MTP) and the effects on reverse cholesterol transport (RCT) in mice. This is the first study to demonstrate the effect of MTP deficiency and inhibition on (macrophage to feces) RCT.

MTP is expressed in several tissues including the liver, intestine, kidney, heart, retina, placenta, and immune cells (5). In the liver and the intestine, MTP is an essential protein for the assembly and secretion of apoB- containing lipoproteins; while its role in other tissues is less clear.

Dikkers et al. determined the extent of RCT in liver-specific MTP (L-MTTP$^{-/-}$) knockout mice and in wild-type mice treated with a pharmacological MTP-inhibitor (BMS-212122) in order to model 'systemic' MTP inhibition. In this study, systemic MTP inhibition resulted in a decrease in intestinal cholesterol absorption concomitant with reduced intestinal expression of NPC1L1. However, curiously, total RCT (macrophage-derived labeled cholesterol to feces transport) was increased in systemic-treated mice, while in contrast it decreased in L-MTTP$^{-/-}$ mice. Increases in biliary sterol excretion did not appear to explain total neutral sterol excretion during systemic MTP inhibition, suggestive of a direct role of the trans-intestinal cholesterol efflux (TICE) pathway in RCT. Traditionally, hepatobiliary cholesterol excretion has been thought to be the main route for cholesterol excretion from the body, but recent reports have demonstrated the phenomenon of TICE; i.e., excretion of cholesterol into the small intestine (6). However, the exact mechanisms involved in TICE are still evolving and controversial.

The first central point of the study by Dikkers et al. is the potential for MTP inhibitors to modulate RCT. The pharmacological MTP inhibitor lomitapide (Juxtapid^{TM}), has been approved recently for use in subjects with familial hypercholesterolemia (7). Lomitapide has been shown to reduce plasma LDL-C and plasma triglyceride concentration by (up to) 50% and 45% respectively (in a multicenter phase III study in patients with familial hypercholesterolemia) (8). Based on the evidence from Dikkers et al., it would be pertinent to determine the contribution of systemic MTP inhibition to RCT in familial hypercholesterolemia subjects. Indeed, the beneficial effects of MTP inhibitors may well extend beyond LDL-C lowering, including the potential to enhance the macrophage RCT and TICE pathways in humans.

The second point that emerges from the study of Dikkers et al. is the potential for pharmacological MTP inhibition to stimulate TICE. Two recent reports (9, 10) have demonstrated that disruption of the lymphatic system leads to an impaired RCT pathway. It is attractive to consider that TICE could be the result of lymphatic drainage of excess sterols during normal homeostasis and RCT (**Fig. 1**). Conversely, the

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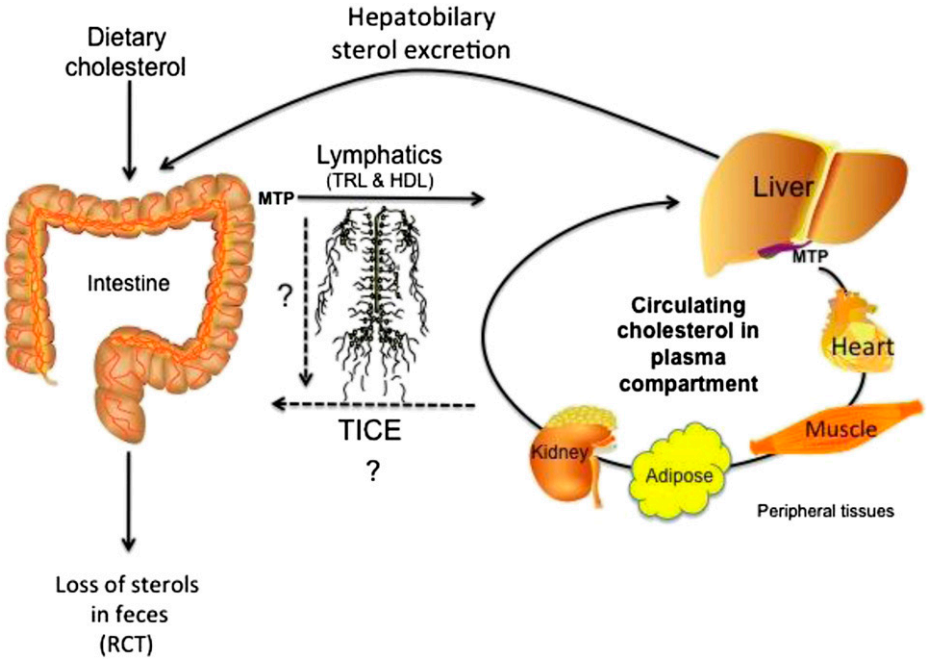

Fig. 1. Plausible pathways of cholesterol flux

presence of a lipid-rich state in the lymphatics (e.g., during the fed state or overproduction of apoB from the intestine during chronic disease states such as obesity and/or diabetes), may confound the ability of protein-protein interactions at the basal-lateral surface and reduce the capacity of TICE to contribute to RCT. The lack of consistent evidence for an effective cholesterol donor to TICE (e.g., HDL) is one of the many unknown factors in appreciating the physiological relevance of this pathway in whole body cholesterol homeostasis in humans (11).

Finally, it is known that hepatotoxicity is a contraindication of pharmacological MTP inhibition that may prove to be rate limiting for widespread use of this therapy (7). Recent studies have shown that intestinal-specific MTP inhibition has beneficial effects on insulin resistance-induced hepatic steatosis (12). Indeed, Dikkers et al. suggest that understanding the impact of intestinal specific MTP inhibition on the RCT pathway may provide key information on the preferable site and effectiveness of MTP inhibition. Some intestinal-specific MTP inhibitors, JTT-130 and SLX-4090, are currently in clinical trials (13).

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