SPECIAL REPORTS AND REVIEWS

New Insights Into the Genetic Regulation of Intestinal Cholesterol Absorption

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The small intestine is a unique organ providing dietary and reabsorbed biliary cholesterol to the body. However, the molecular mechanisms whereby cholesterol is absorbed have not yet been fully understood. Recent research suggests that the newly identified Niemann-Pick C1-like 1 protein (NPC1L1) is expressed at the apical surface of enterocytes and plays a critical role in the absorption of intestinal cholesterol. Furthermore, adenosine triphosphate (ATP)-binding cassette (ABC) transporters ABCG5 and ABCG8 represent apical sterol export pumps that promote active efflux of cholesterol and plant sterols from enterocytes back into the intestinal lumen for excretion. This provides an explanation why cholesterol absorption is a selective process, with plant sterols and other noncholesterol sterols being absorbed poorly or not at all. These findings strongly support the concept that cholesterol absorption is a multistep process, which is regulated by multiple genes at the enterocyte level. The absorption efficiency of cholesterol is most likely determined by the net effect between influx and efflux of intraluminal cholesterol molecules across the brush border of the enterocyte. Combination therapy using a novel, specific, and potent cholesterol absorption (NPC1L1) inhibitor (ezetimibe) and HMG-CoA reductase inhibitors (statins) offers an efficacious new approach to the prevention and treatment of hypercholesterolemia.

Cholesterol homeostasis is mainly maintained by balancing intestinal cholesterol absorption and endogenous cholesterol synthesis with excretion of biliary cholesterol and bile salts. Because elevated serum cholesterol levels are an important risk factor for cardiovascular diseases,[1] extensive studies have been carried out to identify genetic, physical-chemical, and biochemical determinants of intestinal cholesterol absorption.[2,3] Furthermore, the cholesterol carried in low-density lipoprotein (LDL) is derived principally from de novo synthesis and absorption from the diet. In humans, there is a significant and positive correlation between the level of serum LDL-cholesterol and the efficiency of intestinal cholesterol absorption.[4] Thus, pharmacologic control of intestinal cholesterol absorption is potentially an effective way of lowering serum LDL-cholesterol concentrations in the general population. Recent revised treatment guidelines[1] emphasize that individuals at substantial risk for atherosclerosis or patients with cardiovascular diseases should meet defined targets for LDL-cholesterol levels, which has strikingly increased the number of individuals who need cholesterol-lowering therapy. Dietary plant sterols at a dose of 2 g/day have been recommended as adjunctive lifestyle treatment for hypercholesterolemia.[5] However, plant sterols are only minimally soluble in aqueous systems and require formulation for bioactivity. To increase their lipid solubility, it is imperative to esterify plant sterols and to dissolve them at high concentrations in the triglyceride phase of margarines.[6] Recent clinical studies show that plant sterol treatment induces a reduction in serum LDL-cholesterol concentrations in the range of 8% to 14% in persons with mild or moderate hypercholesterolemia.[7] Although statin therapy decreases serum cholesterol concentrations markedly, a high proportion of patients fail to reach the target LDL-cholesterol levels.[8,9] More recently, the discovery and development of ezetimibe,[10,11] a novel, selective, and potent inhibitor that effectively blocks intestinal absorption of dietary and biliary cholesterol, opens a new door to the treatment of hypercholesterolemia.[12–15] This review will focus on the recent progress in the molecular mechanisms of cholesterol absorption and pharmacologic approaches to inhibit the absorption process.

Abbreviations used in this paper: ABC, adenosine triphosphate-binding cassette transporter; ACAT, acyl-CoA:cholesterol acyltransferase; HMG, 3-hydroxy-3-methylglutaryl; LXR, liver X receptor; NPC1L1, Niemann-Pick C1-like 1 protein; QTL, quantitative trait locus; SR-BI, scavenger receptor class B type I; UDCA, ursodeoxycholic acid.

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Physiology of Intestinal Cholesterol Absorption

"Intestinal absorption of cholesterol" is most accurately defined as the transfer of intraluminal cholesterol into intestinal or thoracic duct lymph. Conceptually, absorption needs to be distinguished from "uptake of cholesterol," which refers to entry of cholesterol into intestinal absorptive cells. As can be inferred from these definitions, cholesterol absorption is a multistep process that is regulated by multiple genes.[16,17]

Cholesterol enters the lumen of the small intestine from 3 sources: diet, bile, and intestinal epithelial sloughing. The average daily intake of cholesterol in the Western diet is approximately 300–500 mg. Bile provides 800–1200 mg cholesterol per day to the intraluminal pool. The turnover of intestinal mucosal epithelium establishes a third source of intraluminal cholesterol, which is estimated to contribute 300 mg cholesterol per day. Although the entire length of the small intestine has the capability to absorb cholesterol from the lumen, the main sites of absorption are the duodenum and proximal jejunum.

Cholesterol absorption begins in the stomach when dietary constituents are mixed with lingual and gastric enzymes. The stomach also regulates the delivery of gastric chyme to the duodenum where it is mixed with bile and pancreatic juice. This process continues within the lumen of the small intestine. Some of the lipolytic products, including cholesterol, are nearly insoluble in a pure aqueous system and are therefore dependent on the solubilizing properties of bile salt solutions.[18–22] In contrast, phospholipids, monoacylglycerides, and free fatty acids are readily soluble. Bile salts are biologic amphipathic detergents and can spontaneously form aggregates, ie, simple micelles, when present above a critical micellar concentration. Although simple micelles are able to dissolve lipids,[23] cholesterol is only sparingly soluble in bile salt solutions. The addition of phospholipid or monoacylglyceride to bile salt solutions strikingly augments the solubility of cholesterol by forming mixed micelles.[24,25] Furthermore, excess lipids not dissolved in the micellar phase can be maintained as a stable emulsion by bile salts, phospholipids, monoacylglycerides, and fatty acids in the intestinal lumen.[18,19] During lipolysis, a liquid crystalline phase composed of multilamellar products of lipid digestion forms at the surface of the emulsion droplets.[26,27] This liquid crystalline phase provides an accessible source of cholesterol and other lipids for continuous formation and modification of mixed micelles in the presence of bile salts.

Before cholesterol molecules in the small intestinal lumen can interact with a possible cholesterol transporter(s) for uptake and subsequent transport across the brush border of the enterocyte, they must pass through a diffusion barrier that is located at the intestinal lumen-membrane interface, which may alter the kinetics of cholesterol absorption. This barrier includes an unstirred water layer and a surface mucous coat. Furthermore, the importance of the intestinal mucous coat as a diffusion-limiting barrier has been emphasized because cholesterol molecules could be extensively bound to surface mucins prior to transfer into the enterocyte. It has been observed that physiologic levels of the epithelial mucin encoded by the *Muc1* gene are necessary for normal intestinal uptake and absorption of cholesterol in mice.[28] Because cholesterol absorption efficiency is reduced by ~50% in *Muc1*-deficient mice, there may be alternative pathways for cholesterol absorption. Furthermore, uptake and absorption of cholesterol but not fatty acids is decreased in *Muc1* knockout mice because the movement of big, rigid molecules such as cholesterol crossing the cell membrane is different from that of smaller, less rigid, and space-occupying molecules such as fatty acids. Because the lipid-protein interaction and structural assembly of proteins may influence the kinetics of net cholesterol movement across the cell membrane of enterocyte, it is crucial to investigate how the structural protein integrity or assembly at the level of the cell membrane is maintained during the intestinal absorption of cholesterol. In addition, the unstirred water layer, a series of water lamellae at the interface between the bulk water phase of the lumen and the apical membrane of the enterocyte, is considered to be an important barrier through which a cholesterol molecule in the bulk phase must pass to be absorbed.[29,30] Diffusion through the unstirred water layer is a relatively slow process for cholesterol that is only minimally soluble in aqueous systems. The mixed micelles function as a concentrated reservoir and transport vehicle for cholesterol across the unstirred water layer toward the brush border of the small intestine to facilitate uptake of monomeric cholesterol by the enterocyte.[31]

During the absorption of cholesterol, there is little increase in the cholesterol content of the small intestinal wall, indicating that cholesterol can be rapidly processed and exported from the enterocyte into the intestinal lymph.[2,3] It has been found that, following an intragastric dose of cholesterol, the transport of cholesterol mass and radioactivity in intestinal lymph increases rapidly and peaks after 6–8 hours.[16,17,32,33] After entering the enterocytes, approximately half of the cholesterol molecules move to the endoplasmic reticulum where they