Emerging role of high-density lipoprotein in the prevention of cardiovascular disease

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In major statin trials, the relative risk reduction is typically in the range 25–35%, thus indicating that the majority of cardiac events continues to occur despite statin therapy. Hence, there is a considerable interest in identifying novel therapies capable of further reducing cardiovascular disease risk. One such potential therapeutic target is a low level of high-density lipoprotein (HDL) cholesterol. Emerging targets involved in HDL metabolism are: (i) liver X receptor and peroxisome proliferator-activated receptor agonists; (ii) cholesteryl ester transfer protein inhibitors; (iii) HDL mimetics (ETC-216); (iv) apolipoprotein A-I synthetic peptides; and (v) HDL delipidation and reinfusion. Although they are at various stages of development, each of these therapies has promise for the treatment of cardiovascular disease in humans.

High-density lipoprotein (HDL) cholesterol (HDL-C) concentrations are inversely associated with cardiovascular disease (CVD) risk [1]. HDL and its major protein constituent, apolipoprotein (apo) A-I, are important mediators of reverse cholesterol transport (RCT), a process by which free cholesterol is removed from the peripheral tissues of the body, transferred back to the liver and, ultimately, excreted into the bile [2]. In addition, HDL protects low-density lipoproteins (LDLs) against oxidative modification [3] and has direct anti-inflammatory, antithrombotic and profibrinolytic effects [4–6]. Thus, there are several mechanisms by which HDL could provide protection against CVD.

The current guidelines established by the third Adult Treatment Panel of the National Cholesterol Education Program define a low HDL-C level as <40 mg/dl [7]. Low HDL-C is the most common lipid abnormality observed in patients with known coronary heart disease (CHD), with about a half of CHD patients having this as their primary lipid abnormality [8]. Despite data from large-scale clinical trials indicating that even modest increases in HDL-C concentrations can significantly reduce CHD risk [9,10], well-tolerated drugs with significant HDL-raising potential are still lacking.

Current therapies for increasing HDL-C concentrations

Therapies currently available for increasing HDL-C include fibric acid derivatives, or fibrates, niacin and statins. Fibrates, such as gemfibrozil and fenofibrate, have only modest effects on HDL-C levels, raising them on average by 10–15% [11]. Although niacin can increase HDL-C levels in the order of 15–30%, the doses of niacin required to achieve such increases are often not well tolerated [11]. Statins, the most widely used class of drugs in the treatment of dyslipidemias, are only capable of increasing HDL-C by 5–12% [11,12].

Emerging therapies for reducing cardiovascular disease risk via HDL

ATP-binding cassette transporter A1

A major mechanism by which HDL might protect against the development of atherosclerosis is through

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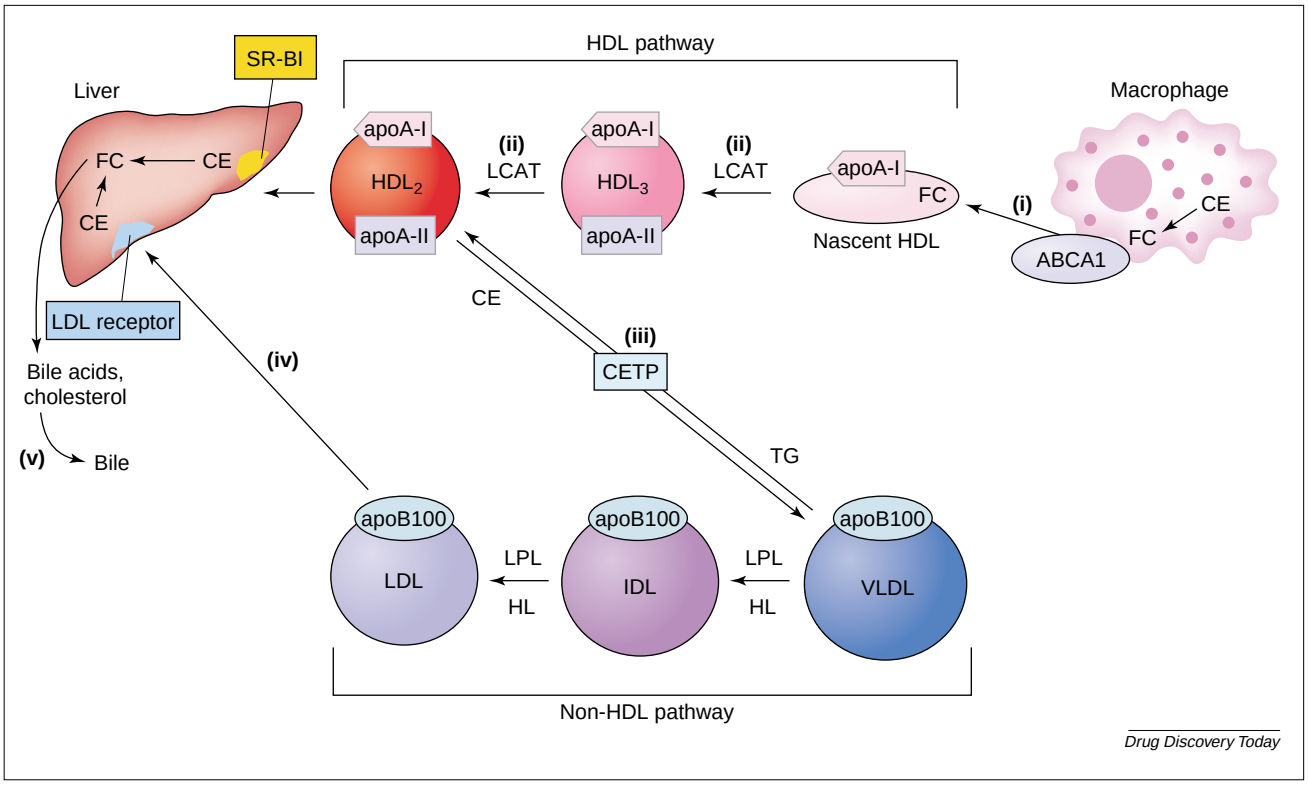

FIGURE 1

Major steps in the reverse cholesterol transport pathway. RCT is a complex process that involves transport proteins, modifying enzymes and cell surface receptors. RCT consists of five main steps: (i) cholesterol efflux from peripheral cells; (ii) cholesterol esterification; (iii) cholesteryl ester transfer; (iv) hepatic cholesterol uptake; and (v) hepatic excretion of cholesterol. In the first step of RCT, ABCA1 mediates the apolipoprotein-stimulated pathway of cholesterol efflux from peripheral cells to lipid-poor HDL. Next, the FC on nascent HDL is esterified by LCAT, generating a spherical HDL particle. LCAT facilitates RCT by decreasing the amount of free cholesterol on HDL, thus maintaining a concentration gradient of cholesterol between HDL and peripheral cells. The third step in RCT is the cholesteryl ester transfer, which is mediated by CETP. This protein promotes the exchange of CE from the HDL pathway to apoB-containing pathway, providing an avenue for uptake of cholesteryl esters by hepatic receptors. The uptake of cholesteryl esters by receptors is the fourth step in RCT. SR-BI is primarily involved in the selective uptake of cholesteryl esters from HDL, whereas the LDL receptor pathway clears those within apoB-containing lipoproteins. The final step in RCT is the excretion of cholesterol by the liver. This can occur directly via the secretion of cholesterol into bile or indirectly by secretion of cholesterol after conversion to bile salts. Abbreviations: CE, cholesteryl esters; FC, free cholesterol; HL, hepatic lipase; IDL, intermediate density lipoprotein; LCAT, lecithin:cholesterol acyltransferase; LPL, lipoprotein lipase; SR-BI, scavenger receptor class BI ; VLDL, very low-density lipoprotein.

its role in RCT (Figure 1). A significant advance in our understanding of this pathway occurred with the identification of mutations in the gene encoding ATP-binding cassette transporter A1 (ABCA1) as the cause of Tangier disease [13–15], a rare genetic disorder characterized by extremely low levels of HDL-C in the plasma and aberrant apolipoprotein-mediated cellular cholesterol efflux [16]. Many studies have now established that ABCA1 mediates the efflux of phospholipids and cholesterol to apolipoprotein acceptors, the initial step in the RCT pathway, and, thus, plays a crucial role in HDL metabolism. This discovery generated great interest in the development of therapies to increase ABCA1 expression.

To date, no therapeutic agents designed to increase ABCA1 expression have been tested in humans. However, evidence from animal studies supports the hypothesis that upregulation of ABCA1 expression might be beneficial in the prevention of atherosclerosis. When fed on an atherogenic diet, C57BL/6 mice that overexpressed human ABCA1 primarily in the liver and in macrophages had significantly (P <0.0005) higher levels of HDL-C (+183%) and apoA-I (+151%) but significantly (P <0.005) lower levels of non-HDL-C (–47%) and apoB (–36%) compared with their nontransgenic littermates [17]. These changes translated into a 65% reduction in mean aortic lesion area in human ABCA1 transgenic C57BL/6 mice relative to controls. By contrast, overexpression of human ABCA1 in an animal model of spontaneous atherosclerosis (the apoE-deficient mouse) had minimal effects on plasma lipoproteins and led to a significant increase in lesion development in male (+160%, P = 0.002) and female (+100%, P <0.001) apoE$^{-/-}$ mice, compared with age- and gender-matched littermates. The results of this study not only indicate that upregulation of ABCA1 might reduce atherogenic risk in humans but also emphasize the important role of apoE in cholesterol metabolism and atherogenesis.

Additional insight into ABCA1 function has been provided by the identification of response elements in the promoter region of the gene [18]. This includes the liver X receptor (LXR)–retinoid X receptor (RXR) promoter