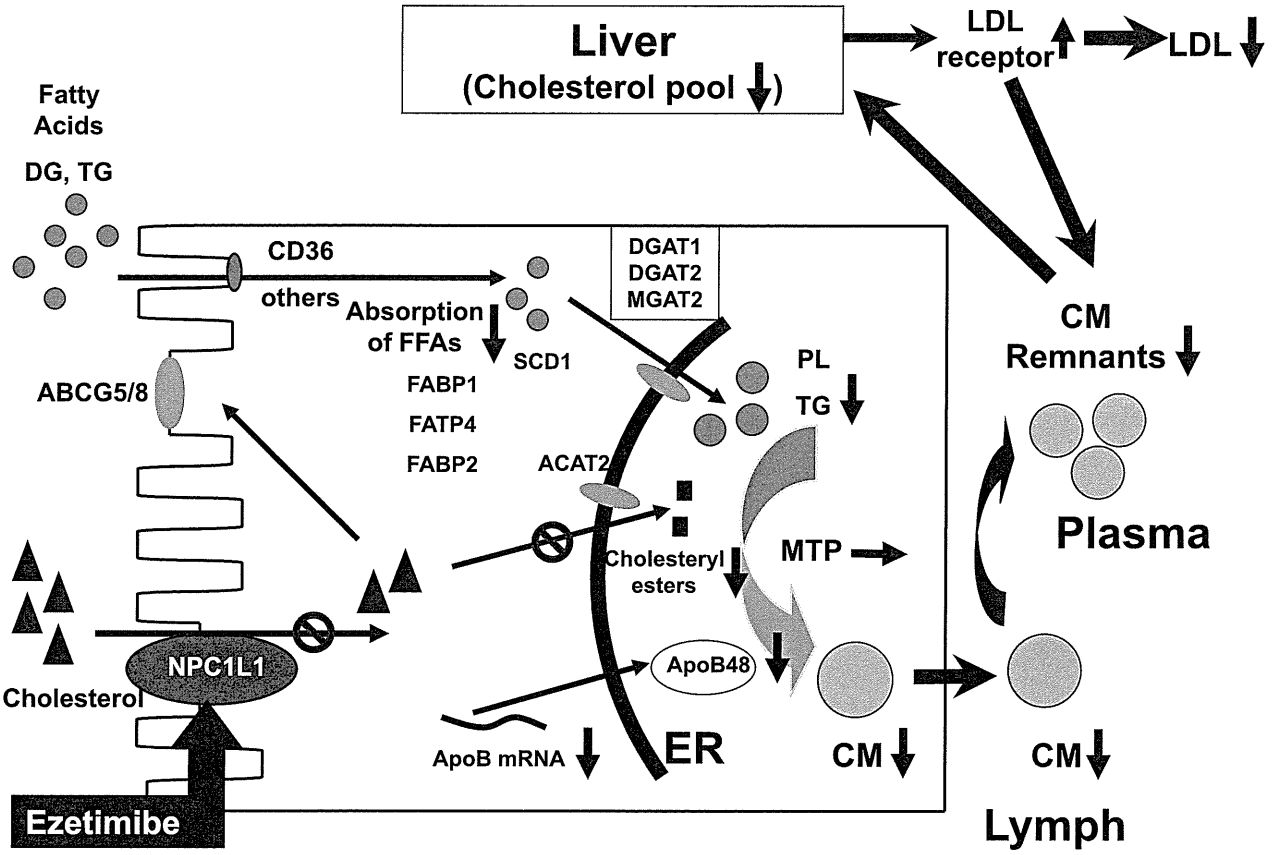

Fig. 28.4 Molecular mechanisms for attenuation of postprandial hyperlipidemia by ezetimibe

(CHD). One study in SR-BI(−/−)/apoE(−/−) mice showed that ezetimibe significantly reduced aortic sinus plaque (57%), coronary arterial occlusion (68%), myocardial fibrosis (57%), and cardiomegaly (12%) compared with untreated controls [62]. Intestinal SR-BI does not impact cholesterol absorption or transintestinal cholesterol efflux in mice [63], and these favorable effects of ezetimibe on atherosclerosis may be attributed to the reduction of cholesterol in the IDL/LDL-size range. The effects of ezetimibe was also evaluated in LDL receptor(−/−)/apoE(−/−) mice [64]. It was demonstrated that functional LDL receptors were not necessary for ezetimibe-mediated reduction of plasma cholesterol or atherosclerosis. In rabbits, ezetimibe was shown to significantly inhibit diet and vascular injury-induced atherosclerosis as measured by intima/media thickness, atherosclerotic lesion composition, and thrombosis. The current preclinical evidence consistently demonstrated that ezetimibe reduces atherosclerosis in animals due primarily to the decrease in atherogenic lipoproteins.

Effect of Ezetimibe on NAFLD in Human Studies

Park et al. [65] treated 45 patients with liver biopsy-proven NAFLD for 24 months with ezetimibe (10 mg/day) in an open-labeled trial and reported reductions in body weight, visceral fat area, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-R), serum TG, total cholesterol, LDL-C, and serum alanine aminotransferase and hsCRP levels. Histological features of steatosis grade, necroinflammatory grade, ballooning score, and NAFLD activity score (NAS) were significantly improved from baseline, whereas the fibrosis stage was not significantly changed.

In another open-labeled pilot study, Yoneda et al. [66] reported improvement of liver histology (NAS and steatosis) in ten NAFLD patients treated with ezetimibe 10 mg daily for 6 months. Chan et al. [67] reported that compared to a hypocaloric, low-fat diet, a combination of hypocaloric, low-fat diet and ezetimibe for 10 weeks decreased intrahepatic TG content (measured by

magnetic resonance imaging) by 18%. However, rigorous, double-blind, placebo-controlled trials are needed to ascertain beneficial effects of ezetimibe in improving NASH/NAFLD.

Potential Therapeutic Targets of Ezetimibe

Potential therapeutic applications of ezetimibe may be patients with type IIa and IIb hyperlipidemia and those with homozygous and heterozygous FH who are very resistant to statin treatment. In patients for secondary prevention of CHD under strong statin treatment, ezetimibe add-on therapy may further lower the levels of serum LDL-C. The first-line therapy of ezetimibe may be targeted to patients with sitosterolemia and those patients who are supposed to have an increased rate of cholesterol absorption, including those with type 2 diabetes, obesity, metabolic syndrome, and CHD. From the point of drug safety, ezetimibe may be used for aged patients and those with chronic kidney disease (CKD). For patients with type IIb, the combination of statins and fibrates may increase the risk of rhabdomyolysis, muscle symptoms, and liver dysfunction. Thus, the combination of ezetimibe with fibrates may be a better tolerated.

Dosing Regimen

During the clinical development of ezetimibe, a wide range of doses of ezetimibe were evaluated, from 0.625 to 40 mg. Five milligram per day of ezetimibe lowered LDL-C significantly, although to a slightly lesser degree than 10 mg/day in some trials [68, 69]. The majority of these trials were done in patients not receiving statins and looked at LDL-C lowering, as opposed to the achievement of National Cholesterol Education Program (NCEP) goals. The usual dose of ezetimibe was set at 10 mg/day, but 5 mg/day dose was reported to significantly reduce LDL-C levels [70]. The effect of ezetimibe on LDL-C levels reaches the maximum with 10 mg/day dose and no more additional LDL-C lowering effect is observed.

Risks and Precaution

Prescribing Information

Ezetimibe (ZETIA) is prescribed as one 10-mg tablet once daily, with or without food. Dosing should occur either ≥2 h before or ≥4 h after administration of a bile acid sequestrant.

The data of clinical trials of 6–48 week durations showed that ezetimibe administered alone or in combination with statins was generally well tolerated with safety profiles similar to those of placebo or statins in patients with hypercholesterolemia and in high-risk populations [71]. Adverse events were not observed with combination ezetimibe + statins compared with statin monotherapy in a meta-analysis of 18 randomized clinical trials (n=14,497) [72], and in a pooled analysis of 16 studies (n=14,471) in patients aged 65–74 and 75 years or older [73].

In studies with longer durations of 2 years or more (n=12,313), the incidence of adverse events was similar for ezetimibe + statins compared with placebo or statin alone [74]. There were no significant differences in adverse events for gastrointestinal symptoms, hepatic dysfunction, and gall-bladder-related diseases, allergic reactions, or creatine kinase elevations. In the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) Trial, a significant increase in the rate of liver enzyme elevations was reported in the ezetimibe + simvastatin group compared with placebo, however, this was within the range of adverse event rates reported for the combination [75].

In the SEAS Trial, increased numbers of incident and fatal cancers were noted in the ezetimibe + simvastatin group compared with the placebo group. However, an independent meta-analysis of interim safety data from Study of Heart and Renal Protection (SHARP) Trial and IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT; ~20,000 patients) showed that ezetimibe+simvastatin treatment did not increase the risk of cancer [76]. Furthermore, the SHARP study showed an identical incidence of cancers in the ezetimibe + simvastatin and placebo groups. Taken together, ezetimibe alone or in combination with statins is well tolerated and safe.

Drug Interactions and Compatibilities

Some medications for cholesterol lowering should not be taken at the same time. These drugs include cholestyramine, colestipol, colesevelam, or colestimide. Before taking ezetimibe, the patients have to wait at least 4 h after taking any of these medicines. Patients may also take ezetimibe 2 h before taking any of these other medicines. In contrast, ezetimibe may be taken at the same time with fenofibrate or with any of statins.

If patients are allergic to ezetimibe, if they have liver disease, or if they have any of these other conditions, they may need a dose adjustment or special tests to safely use ezetimibe (kidney disease, a thyroid disorder, or when using corticosteroids or hormones including birth control pills). Rhabdomyolysis or muscle symptoms are reportedly very rare for ezetimibe. Food and Drug Administration (FDA) pregnancy category for ezetimibe is C. It is not known whether ezetimibe is harmful to an unborn baby, therefore administration of ezetimibe to pregnant women should be avoided. It is not known whether ezetimibe passes into breast milk or if it could harm a nursing baby. Administration of ezetimibe to breast-feeding women should be avoided. Older adults may be more likely to have side effects from this medicine.

Clinical Trials for Prevention of Atherosclerotic Cardiovascular Disease (CVD)

Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) Trial (ClinicalTrials.gov, NCT00552097)

ENHANCE Trial [77] is the first clinical trial of ezetimibe. It is a double-blind, randomized, 24-month trial comparing the effects of daily therapy with 80 mg of simvastatin with placebo or 10 mg of ezetimibe in 720 patients with heterozygous FH. The intima-media thickness (IMT) of walls of carotid and femoral arteries of the patients were assessed by B-mode ultrasonography. The primary outcome measure was the change in the mean carotid-artery IMT, which was defined as the average of the means of the far-wall IMT of right and left common carotid arteries, carotid bulbs, and internal carotid arteries. At the end of the study, the mean LDL-C level was 192.7 mg/dl in the simvastatin group and 141.3 mg/dl in the combined-therapy group with a statistically significant 16.5% reduction. The differences between the two groups in reductions in levels of TG and hsCRP were 6.6 and 25.7%, respectively, with significant greater reductions in the combined-therapy group. However, the primary outcome, the mean change in the carotid-artery IMT, was not significantly different between the simvastatin group and simvastatin + ezetimibe group. Secondary outcomes, consisting of other variables regarding the IMT of carotid and femoral arteries, also did not differ significantly between the two groups. Thus, in FH heterozygotes, combined therapy with ezetimibe and simvastatin did not reduce IMT compared with simvastatin alone, despite decreases in LDL-C and hsCRP. The results of this study were disappointing, however the mean IMT of carotid arteries before treatment was very thin (mean 0.69 mm) compared with that usually seen in FH heterozygotes of this age. Therefore, similar studies are strongly recommended for FH heterozygotes with thicker IMT.

Simvastatin and Ezetimibe in Aortic Stenosis Trial (ClinicalTrials.gov, NCT00092677)

SEAS Trial [75] is a randomized, double-blind trial involving 1873 patients with mild-to-moderate, asymptomatic aortic stenosis who received 40 mg/day of simvastatin plus either 10 mg/day of ezetimibe or placebo daily. The primary outcome was a composite of major cardiovascular events, including death from cardiovascular causes, aortic valve replacement, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, heart failure, coronary artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke. Secondary

outcomes were events related to aortic valve stenosis and ischemic cardiovascular events. During a median follow-up of 52.2 months, the primary outcome occurred in 35.3% of patients in the simvastatin-ezetimibe group and in 38.2% of patients in the placebo group (not significant), respectively. Aortic valve replacement was performed in 28.3% of patients in the simvastatin-ezetimibe group and in 29.9% of patients in the placebo group (not significant), respectively. Fewer patients had ischemic cardiovascular events in the simvastatin-ezetimibe group than in the placebo group (hazard ratio, 0.78; 95% CI, 0.63 to 0.97; $P=0.02$), mainly because of smaller number of patients who underwent coronary artery bypass grafting. Cancer occurred more frequently in the simvastatin-ezetimibe group, although later meta-analysis revealed that ezetimibe did not increase the risk of cancer [76]. Thus, simvastatin and ezetimibe did not reduce the composite outcome of combined aortic valve events and ischemic events in patients with aortic stenosis. However, it was indicated that such therapy may reduce the incidence of ischemic cardiovascular events but not events related to aortic valve stenosis.

Stop Atherosclerosis in Native Diabetics Study (SANDS) Trial (ClinicalTrials.gov, NCT00047424)

It has not been clarified whether the addition of ezetimibe to statin therapy affects subclinical atherosclerosis. The secondary analysis from the SANDS Trial examined the effects of lowering LDL-C with statins alone versus statins plus ezetimibe on common carotid artery intima-media thickness (CIMT) in patients with type 2 diabetes and no prior cardiovascular event [78]. Within an aggressive group (target LDL-C≤70 mg/dl; non-HDL-C≤100 mg/dl; systolic blood pressure ≤115 mmHg), change in CIMT over 36 months was compared in diabetic individuals >40 years of age receiving statins plus ezetimibe versus statins alone. The CIMT changes in both aggressive subgroups were compared with changes in the standard subgroups (target LDL-C≤100 mg/dl; non-HDL-C≤130 mg/dl; systolic blood pressure ≤130 mm Hg). Mean LDL-C was reduced by 31 and 32 mg/dl in the aggressive group receiving statins plus ezetimibe and statins alone, respectively, compared with changes of 1 mg/dl in the standard group ($p<0.0001$) versus both aggressive subgroups. Within the aggressive group, mean CIMT at 36 months regressed from baseline similarly in the ezetimibe (−0.025 [−0.05–0.003] mm) and nonezetimibe subgroups (−0.012 [−0.03–0.008] mm), but progressed in the standard treatment arm (0.039 [0.02–0.06] mm), intergroup $p<0.0001$). Thus, reducing LDL-C to aggressive targets resulted in similar regression of CIMT in patients who attained equivalent LDL-C reductions from a statin alone or statin plus ezetimibe. CIMT increased in those achieving standard targets.

The Study of Heart and Renal Protection Trial (ClinicalTrials.gov, NCT00125593, and ISRCTN54137607)

Although lowering LDL-C with statin therapy has been shown to reduce the incidence of myocardial infarction, ischemic stroke, and the need for coronary revascularization in people without kidney disease, it remains uncertain whether it is beneficial among people with CKD. The SHARP Trial [74] assessed the efficacy and safety of the combination of simvastatin plus ezetimibe in patients with CKD. This is a randomized double-blind trial, including 9270 patients with CKD (3023 on dialysis and 6247 not) without known history of myocardial infarction or coronary revascularization. Patients were randomly assigned to simvastatin 20 mg plus ezetimibe 10 mg daily versus placebo. The primary outcome was the first major atherosclerotic event (nonfatal myocardial infarction or coronary death, nonhemorrhagic stroke, or any arterial revascularization procedure). Four-thousand six-hundred fifty patients were assigned to receive simvastatin + ezetimibe and 4620 to placebo. Allocation to simvastatin + ezetimibe yielded an average LDL-C difference of 0.85 mmol/L (with about two-thirds compliance) during a median follow-up of 4.9 years and

produced a 17% proportional reduction in major atherosclerotic events with simvastatin + ezetimibe versus placebo. Nonsignificantly fewer patients allocated to simvastatin+ezetimibe had a nonfatal myocardial infarction or died from CHD. There were significant 25% reductions in nonhemorrhagic stroke and 21% decrease in arterial revascularization procedures, respectively. These effects were consistent among subgroups of patients evaluated including dialysis and nondialysis patients. The reduction of cardiovascular events was proportional to the observed degree of LDL-C lowering, consistent with expectations from the Cholesterol Treatment Trialists' meta-analysis of statin trials in patients without CKD [79]. Thus, reduction of LDL-C with simvastatin 20 mg+ ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced CKD.

Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER6-HALTS) Trial (ClinicalTrials.gov, NCT00397657)

The ARBITER 6-HALTS Trial [80] was terminated early on the basis of a prespecified interim analysis showing superiority of niacin over ezetimibe on change in CIMT. Patients with CHD or CHD equivalent with LDL-C<100 mg/dl and HDL-C<50 mg/dl for men or 55 mg/dl for women while receiving stable statin treatment were randomly assigned to ezetimibe (10 mg/day) or extended-release niacin (target dose, 2000 mg/day). The primary end point was change in mean CIMT. Three-hundred and fifteen patients (208 with 14-month follow-up and 107 after mean treatment of 7±3 months) were included. Niacin (n=154) resulted in significant reduction (regression) in mean CIMT (−0.0102±0.0026 mm; p<0.001) and maximal CIMT (−0.0124±0.0036 mm; p=0.001), whereas ezetimibe (n=161) did not reduce mean CIMT (−0.0016±0.0024 mm; p=0.88) or maximal CIMT (−0.0005±0.0029 mm; p=0.88) compared with baseline. There was a significant difference between ezetimibe and niacin treatment groups on mean changes in CIMT, favoring niacin, for both mean CIMT and maximal CIMT. Increased cumulative drug exposure was related to regression of CIMT with niacin, and progression of CIMT with ezetimibe. In this trial, niacin-induced regression of CIMT and was superior to ezetimibe for patients taking statins.

Ongoing Clinical Trials

Recently, the results of IMPROVE-IT (The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) [81] have been reported at the annual meeting of the American Heart Association in Chicago (November 2014). Although the final paper has not been published yet, the results are available at the AHA website. IMPROVE-IT is a multicenter, randomized, double blind trial to evaluate the potential benefit for reduction in major cardiovascular (CV) events from the addition of 10 mg/day ezetimibe versus placebo to 40 mg/day of simvastatin therapy in 18,144 patients who present with acute coronary syndromes (ACS). Their LDL-C levels were 50-125 mg/dL (statin naïve) or 50-100 mg/dL if they have been treated with prior lipid lowering therapy. The simvastatin dose was uptitrated to 80 mg if LDL-C were more than 79 mg/dL in a double-blind fashion in both treatment groups. The primary endpoint was first occurrence of CV death, nonfatal myocardial infarction (MI), rehospitalization for unstable angina, coronary revascularization (≥30 days following randomization) or stroke. Patients were followed for minimum 2.5 years and until ≥5250 patients experienced a primary endpoint.

The mean LDL-C was significantly lower in patients treated with simvastatin and ezetimibe relative to those treated with simvastatin and a placebo (53.2 mg/dL vs. 69.9 mg/dL at one year, median time average 53.7 mg/dL vs 69.5 mg/dL). Relative to simvastatin with a placebo, simvastatin with 10 mg/d of ezetimibe reduced ischemic stroke by 21% and MI by 13%, respectively, and resulted in a significantly lower incidence of the primary combined endpoint (34.7% vs. 32.7%,

P=0.016, NNT=50). On-treatment analysis also confirmed the effects of ezetimibe on CV events. The safety of ezetimibe on simvastatin was also established. IMPROVE-IT is the first trial demonstrating an incremental clinical benefit by adding a non-statin agent to statin therapy and reaffirming the LDL hypothesis stating that reduction of LDL-C prevents CV events and even lower LDL-C is better.

In Japan, Ezetimibe Lipid Lowering Trial on Prevention of Atherosclerosis in 75 or Older (EWTOPIA75) is now ongoing. This study includes 6000 high LDL-C (≥140 mg/dl) patients aged 75 years or older who do not have prior CHD but have coronary risks such as diabetes mellitus and hypertension. The patients will be treated either with diet therapy alone or with diet therapy plus ezetimibe (10 mg daily). The primary endpoint is a composite of cardiovascular events and stroke. This study will reveal for the first time the significance of ezetimibe alone in aged patients with high risk.

Conclusion

Ezetimibe is a specific inhibitor of NPC1L1, inhibits the absorption of cholesterol, plant sterols, and oxidized cholesterol. This chapter summarized the most recent information on the pleiotropic effects of ezetimibe in addition to the reduction of LDL-C. Especially, ezetimibe exerts additional effects on TRL and postprandial hyperlipidemia, absorption of FFA from the small intestines, and thereby reduce hepatic steatosis. It should be clarified in future studies whether these actions translate into clinical benefit in prevention of atherosclerotic CVD.

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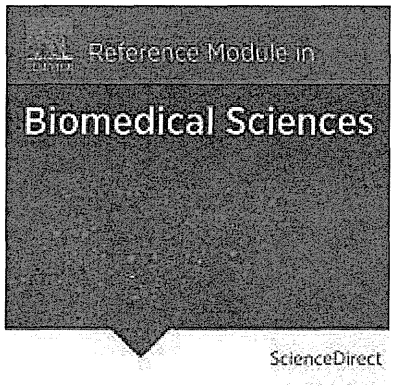

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Low HDL and High HDL Syndromes☆

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Glossary

Apolipoprotein Lipoprotein associated proteins that play a critical role in the structure, solubility, antigenicity, transport, enzyme activation, and cellular uptake of lipoproteins.

Atherosclerosis A common form of arteriosclerosis in which deposits of yellow plaques containing cholesteryl esters, and lipid-laden macrophages (foam cells) are formed with large and medium-sized arteries.

Hepatic Relating to or affecting the liver.

Lecithin A phosphoglyceride that is the major component of cell membranes, consisting of esters of glycerol with two molecules of long-chain aliphatic acids and one of phosphoric acid.

☆*Change History:* December 2014. S Yamashita and Y Matsuzawa updated all the text and references.

Introduction

Plasma high-density lipoprotein cholesterol (HDL-C) level was shown to correlate negatively with the incidence of coronary heart disease (CHD). Low HDL syndrome is a condition in which plasma HDL-C is low, is a dyslipidemia frequently observed in patients with premature coronary heart disease (CHD).

The anti-atherogenic functions of HDL have been demonstrated by a number of experiments *in vitro* and *in vivo*. The injection of HDL and its major apolipoprotein (apo) constituent, apo A-I, has been shown to attenuate atherosclerosis in some animal models. Lipid-poor apo A-I and HDL remove cholesterol from cultured lipid-laden macrophages via ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1), respectively. The cholesterol is esterified by lecithin:cholesterol acyltransferase (LCAT) to form cholesteryl ester (CE). The CE of HDL is subsequently transferred by plasma cholesteryl ester transfer protein (CETP) to very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) in exchange for triglycerides (TG). The TG in HDL is hydrolyzed by hepatic triglyceride lipase (HL) and HDL becomes smaller to take up more cholesterol. Furthermore, the IDL and LDL are taken up by hepatic LDL receptor. The CE of HDL particle is taken up by the liver via scavenger receptor class B type I (SR-BI). Thus, excess cholesterol in the foam cells of arteries is transported back to the liver, a process called 'reverse cholesterol transport (RCT)' (Figure 1). In the liver, cholesterol is catabolized into bile acid and excreted into the bile.

The plasma levels of HDL-C as well as the biochemical composition and functions of HDL particles are regulated by apolipoproteins, lipolytic enzymes, lipid transfer proteins, receptors, and cellular transporters such as ABCA1 and ABCG1. Furthermore, transcription factors such as liver X receptor (LXR) and farnesoid X receptor (FXR) that regulate the expression of ABCA1 and ABCG1 are also involved in the regulation of plasma HDL-C levels. Low HDL syndrome is caused by abnormalities of a variety of molecules involved in RCT.

The etiology of high HDL syndrome is also based upon abnormalities in the molecules involved in RCT. In contrast to low HDL syndrome, the story of high HDL syndrome is somewhat complicated. Although high HDL syndrome was previously believed to be associated with a longevity due to a reduced incidence of CHD, Matsuzawa et al. reported two hyperalphalipoproteinemic (HALP) cases with premature corneal opacity and in one case angina pectoris, and proposed that high HDL syndrome is heterogeneous, not always beneficial, and sometimes rather atherogenic. Recently, evidence supporting this proposal has been accumulated from many experimental and epidemiological studies.

In the current review, we summarize the clinical characteristics and pathophysiology of low HDL syndrome and high HDL syndrome and the dynamics and efficiency of RCT in these conditions are discussed. Due to limitations of space, many data on genetically engineered mice with altered levels of plasma HDL-C are not discussed.

Factors Regulating Plasma HDL-Cholesterol Levels

HDL particles consist of heterogeneous subclasses. They have a density range of 1.063–1.21 g ml^{-1} and are small in size (Stokes' diameter: 5–17 nm). They consist of approximately 50% lipids and 50% proteins. HDL can be classified by density (HDL_2 or HDL_3 fraction), electrophoretic mobility (α- and pre-β-electrophoretic mobility), and apolipoprotein composition (Lp A-I or Lp A-I/A-II). The quantity and quality of HDL particles are regulated by many factors, such as plasma enzymes, lipid transfer proteins, and cell surface receptors as well as transporters.

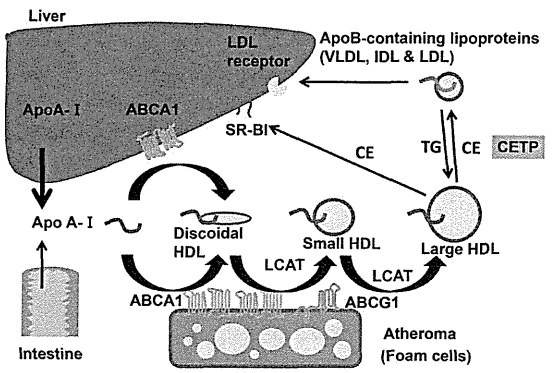

Figure 1 Metabolic map of apo A-I and HDL-mediated reverse cholesterol transport in humans. Arrows denote cholesterol transport in the human body mediated by lipoproteins, plasma lipid transfer proteins, and cell surface receptors and transporters. Cholesterol efflux from peripheral cells is thought to be very diverse. There are some candidates for cell surface receptors, such as ABCA1 and ABCG1.

Synthesis and Secretion of HDL

The major constituent of HDL, apo A-I, is synthesized in the liver (~80%) and small intestines (~20%). ABCA1 interacts with apo A-I and is involved in efflux of cholesterol and phospholipids on the plasma membrane, generating 'discoidal nascent HDL' particles. The genetic deficiency of ABCA1 causes Tangier disease characterized by an enhanced atherosclerosis, hepatosplenomegaly and orange tonsils due to massive deposition of CE in tissues. Transporters such as ABCG1 and other molecules may be involved in HDL-mediated cholesterol efflux, although ABCA1 is requisite for the apo A-I-mediated production of HDL particles. Free cholesterol on nascent HDL particles is esterified to form CE by the action of LCAT. LCAT plays a pivotal role in making HDL particles spherical and mature.

Modification of HDL Particles in Plasma

Several enzymes are involved in the modifying the quality and quantity of HDL particles in plasma. The movement of lipids and apoliporoteins during lipolysis is one of the important sources for HDL particles. Two lipases, lipoprotein lipase (LPL) and hepatic triglyceride lipase (HL), are involved in the lipolysis of chylomicrons/chylomicron remnants/VLDL and IDL, respectively. The hydrolysis of TG-rich lipoproteins by these lipases releases some apolipoproteins, cholesterol and phospholipids into plasma, and these constituents can be used for the formation of new HDL particles. Plasma phospholipid transfer protein (PLTP) transfers phospholipids and cholesterol from apo B-containing lipoproteins to HDL. HL, located on the liver sinusoid, is thought to remodel large and TG-rich HDL particles into smaller less TG-rich ones.

As mentioned earlier, plasma CETP facilitates the transfer of neutral lipids between lipoproteins. CETP transfers CE from HDL to apo B-containing lipoproteins in exchange for TG from apo B-containing lipoproteins to HDL. Plasma CETP deficiency causes a marked elevation of plasma HDL-C levels.

Endothelial lipase (EL) is a phospholipase belonging to the LPL family, which includes LPL and HL. In contrast to LPL and HL, EL mainly regulates HDL metabolism and HDL-C levels in humans and mice. The inhibition of EL may increase the HDL-C level. EL hydrolyzes the phospholipids in HDL and is involved in the remodeling of HDL particles. Although the inhibition of EL activity leads to elevation of HDL-C levels, it has not been established in humans whether EL inhibition may attenuate atherosclerosis.

Hepatic Uptake of HDL and HDL Lipids

As the last step of RCT, at least two distinct pathways are involved in taking up cholesterol from plasma. One is the LDL receptor-mediated pathway and the other is the HDL receptor(s)-mediated pathway. Although the impact and significance of this pathway are not completely understood in humans, SR-BI is the physiologically relevant hepatic HDL receptor established in mice. SR-BI mediates the selective uptake of CE in HDL. There may be other possible pathways, in which whole particles of HDL are taken up and catabolized.

Degradation of Apo A-I or HDL Particles

In the kidney, apo A-I is catabolized by a size-dependent filtration process. Cubilin is thought to mediate the reabsorption of apo A-I from the renal proximal tubule lumen.

Multiple Functions of HDL and Apo A-I

Recently, HDL and apo A-I have been speculated to have a variety of functions, including anti-oxidative, anti-inflammatory, anti-thrombotic, anti-apoptotic, anti-diabetic, anti-infectious, endothelial cell-repairing, vascular endothelial function-improving effects in addition to cellular cholesterol efflux and RCT. These effects may be comprehensively involved in the prevention of atherosclerosis progression.

Recent proteomic analysis of HDL by mass spectrometry identified that HDL is associated with more than 85 proteins. In addition to proteins consistent with traditionally accepted roles in lipid transport, HDL carries unique constituents such as protease inhibitors involved in hemostasis, acute-phase response proteins, immune function mediators, complement pathway members and metal-binding proteins. This compositional diversity of HDL may suggest the pleiotropic functions of HDL, including roles in lipid transport, oxidation, inflammation, hemostasis, and immune system.

Functional HDL and Dysfunctional HDL

As mentioned earlier, HDL is known to modulate systemic inflammation and is thus anti-inflammatory (functional HDL). In the absence of inflammation, HDL has a complement of antioxidant enzymes that work to maintain an anti-inflammatory state. Conversely, in the presence of systemic inflammation, antioxidant enzymes can be inactivated, resulting in the accumulation of oxidized lipids and proteins that may make HDL proinflammatory (dysfunctional HDL) and increase vascular inflammation. Under these conditions, the apo A-I of HDL particles can be modified by reactive oxygen species. This oxidative modification impairs the ability of HDL to promote cholesterol efflux via ABCA1 and ABCG1. HDL may be a shuttle that can be either

anti-inflammatory or proinflammatory, depending on its cargo of proteins, enzymes, and lipids. Under some conditions, HDL can become dysfunctional and even proinflammatory, but this characterization can change with resolution of systemic inflammation or use of certain treatments.

Animal and human studies suggested that measures of the quality and novel functions of HDL might provide an improved means of identifying subjects at increased risk for atherosclerotic events, compared with the current practice of only measuring HDL-C levels. Therapeutic approaches that reduce coronary risk, such as statins and lifestyle changes, can favorably moderate the characteristics of proinflammatory HDL. Furthermore, apo A-I mimetic peptides, delipidated HDL and other compounds that target functional aspects of HDL may provide novel approaches to reduce cardiovascular risk.

Low HDL Syndrome

Primary Low HDL Syndrome

The etiology of low HDL syndrome can be divided into two; primary low HDL syndrome and secondary low HDL syndrome. The primary or secondary abnormalities in molecules involved in RCT may cause low HDL syndrome. Table 1 shows the comparison of clinical and biochemical characteristics of primary low HDL syndrome.

Familial LCAT deficiency and fish eye disease

Both familial LCAT deficiency and fish eye disease (FED) are caused by the mutations in the LCAT gene. Both disorders lead to a marked reduction in plasma HDL-C. Since LCAT catalyzes the esterification of free cholesterol on HDL, its deficiency results in accumulation of free cholesterol, but not CE, in a variety of tissues, including cornea and kidneys. Thus, the plasma CE ratio (CE divided by total cholesterol) is markedly reduced. The lipoproteins of familial LCAT deficiency are morphologically abnormal, with the appearance of multilamellar vesicles, rouleaux, LpX-like particles. The major clinical symptoms in familial LCAT deficiency are corneal opacities, anemia (red blood cells appear as acanthocytes), and proteinuria, which may eventually progress to renal failure in cases with a total deficiency of LCAT. Foam cells accumulate in a variety of tissues, including cornea, kidney, liver, spleen, and arteries. Interestingly, patients with familial LCAT deficiency are usually not accompanied by premature CHD.

Patients with FED or partial LCAT deficiency presented with no clinical signs such as nephropathy except for the characteristic dense age-dependent corneal opacities. The patients are characterized by HDL deficiency and elevated TG levels. They demonstrate an apparently normal activity of LCAT enzyme to esterify cholesterol in plasma, a partial reduction in LCAT concentration, and a nearly normal cholesterol esterification rate. Although the CE content of HDL was extremely low, the relative CE content of VLDL and LDL was normal. It was thus postulated that LCAT exhibits two activities: alpha-LCAT activity specific for HDL that migrate with alpha-mobility upon gel electrophoresis, and beta-LCAT activity specific for pre-beta and beta-migrating lipoproteins (VLDL and LDL, respectively). Thus, FED was classified as alpha-LCAT deficiency whereas familial LCAT deficiency was due to the lack of both alpha- and beta-LCAT activities. However, after cloning of the LCAT gene, alpha- and beta-LCAT activity represented two functional aspects of the same protein in humans.

Table 1 Comparison of clinical and biochemical characteristics of primary low HDL syndrome

Affected gene	*Tangier disease* *ABCA1*	*Familial HDL deficiency without Tangier disease phenotype* *ABCA1 (some cases)*	*Familial LCAT deficiency* *LCAT*	*Fish eye disease* *LCAT*	*ApoA-I deficiency* *apoA-I*
Clinical signs and symptoms					
Typical Tangier phenotype (orange tonsils, hepatosplenomegaly, neuropathy)	+	–	–	–	–
Corneal opacity	+	+	+++	+++	++
Nephropathy	–	–	+	–	–
Risk for coronary heart disease	Moderately increased	Moderately increased	Normal/ increased	Normal/ increased	Increased
Biochemical data					
Plasma total cholesterol	Low	Low	Low	Low	Normal
LDL-cholesterol	Low	Normal	Normal	Normal	Normal
HDL-cholesterol	None	None	Very low	Very low	None
Plasma triglycerides	Increased	Normal	Increased	Increased	Normal
% Cholesteryl ester	Normal	Normal	Low	Low	Normal
Apolipoprotein (apo) A-I	Very low	Very low	Very low	Very low	None
Relative increase in apo apo A-I precursor	+	+	–	–	–
α-LCAT activity	Normal	Normal	Very low	Very low	Normal
Cell biological data					
Cholesterol efflux from cells (apo A-I-mediated)	Absent	Absent	Normal	Normal	Normal

Apo A-I genetic mutations and polymorphisms affecting HDL-cholesterol levels

The human *apo A-I* gene is located on chromosome 11 in a cluster with two other apolipoprotein genes, *apo C-III* and *apo A-IV*. Various disruptions and mutations of the *apo A-I* gene have been reported. Some *apo A-I* gene mutations caused a marked deficiency of plasma HDL-C levels as observed in patients with a genetic deficiency of ABCA1 or LCAT and are associated with premature CHD. However, HDL-deficient patients with *apo A-I* mutation do not usually show anemia, proteinuria, orange tonsils, hepatosplenomegaly and premature CHD. Some mutations or polymorphisms in the *apo A-I* gene are related to the phenotypic expression of amyloidosis and neuropathy.

Secondary Low HDL Syndrome

Smoking

Low HDL-C syndrome is often observed in subjects who smoke. The reduction of plasma HDL-C by smoking is supposed to be due to the reduced activity of LCAT. Cessation of smoking results in an elevation of plasma HDL-C levels.

Physical inactivity

Low HDL-C syndrome is also observed in subjects who are physically inactive. The mechanism for the decrease of plasma HDL-C by physical inactivity is supposed to be related to the reduced activity of LPL. Aerobic exercise is known to increase HDL-C levels.

Hypertriglyceridemia

Patients with hypertriglyceridemia are often associated with the reduction of plasma HDL-C, but hypertriglyceridemic subjects do not always show the reduction of HDL-C. Hypertriglyceridemia appears to stimulate the lipid exchange and accelerate the catabolism of HDL protein. Reduced activity of plasma lipolytic enzymes causes the impaired catabolism of TG-rich lipoproteins, leading to a reduction of the source of lipids for generating new HDL particles. Patients with low HDL-C have a higher risk for CHD, but a combination of hypertriglyceridemia and low HDL-C is highly atherogenic and markedly increases the CHD risk. The treatment of hypertriglyceridemia by fibrates and nicotinic acids usually increases plasma HDL-C levels.

Visceral fat obesity and metabolic syndrome (insulin resistance syndrome)

Low HDL-C syndrome is often observed in patients with visceral fat obesity. Even in non-obese patients with the metabolic syndrome due to visceral adiposity, plasma HDL-C level is usually low. The reduction of plasma HDL-C in these subjects may be partly attributed to hypertriglyceridemia and reduction of adiponectin that was shown to increase the hepatic synthesis of HDL via induction of hepatic ABCA1 and apo A-I protein and enhance the cholesterol efflux from macrophages via induction of macrophage ABCA1 protein. After reduction of body weight in patients with visceral fat obesity or the metabolic syndrome, plasma HDL-C is usually increased.

Patients with a genetic deficiency of long-chain fatty acid transporter CD36 are often associated with insulin resistance and a clustering of multiple risk factors such as hypertriglyceridemia and low HDL-C levels.

Inflammation

Plasma HDL-C level may be a negative marker for systemic or local inflammation. Some pathological conditions with chronic or acute systemic inflammation (e.g., severe infection and hematological malignancy) are associated with a reduction of HDL-C along with increased serum amyloid A proteins. Several studies have indicated that low HDL-C may be a marker for cardiac events during short-term follow-up in association with an increase in high-sensitivity C-reactive protein (hsCRP).

Cholestatic disorders

In obstructive liver diseases such as end-stage liver cirrhosis, plasma HDL-C levels may be markedly reduced to the same extent as in primary HDL deficiency. The reduction of HDL-C is based upon the decrease in hepatic protein synthesis including LCAT.

Drugs

Some drugs, such as androgens, progesterone, anti-hypertensive drugs (thiazides and beta blockers) or an anti-hyperlipidemic drug, probucol, are known to decrease plasma HDL-C levels. Probucol is a potent antioxidant and anti-hyperlipidemic drug that attenuates xanthelasma and xanthoma formation even in patients homozygous for familial hypercholesterolemia and in Watanabe heritable hyperlipidemic rabbits. Although probucol reduces HDL-C, probucol has a variety of anti-atherogenic functions, which will be discussed later.

High HDL Syndrome

Primary High HDL Syndrome

Etiologies for high HDL syndrome are listed in Table 2.

Table 2 Primary and secondary high HDL syndrome

Primary high HDL syndrome
Familial cholesteryl ester transfer protein (CETP) deficiency
Familial hepatic triglyceride lipase (HL) deficiency
Familial hyperalphalipoproteinemia with premature corneal opacity (Combined deficiency of CETP and HL activity)
Familial hyperalphalipoproteinemia with genetic abnormalities in scavenger receptor class B type I (SR-BI) gene
Familial hyperalphalipoproteinemia with genetic abnormalities in endothelial lipase (EL) gene
Familial hyperalphalipoproteinemia with increased production of apo A-I
Familial hyperalphalipoproteinemia with reduced uptake of HDL by lymphocytes
Secondary high HDL syndrome
Chronic heavy alcohol consumption
Primary biliary cirrhosis
Inhibitors of CETP in plasma
Multiple symmetric lipomatosis
Chronic obstructive pulmonary disease (COPD)
Aerobic exercise
Drugs
Insulin
Estrogen and derivertives
Glucocorticoids
HMG-CoA reductase inhibitor (statins)
Intestinal cholesterol transporter inhibitor (ezetimibe)
Fibrates
Nicotinic acid and its derivatives
Cyclosporin
etc.

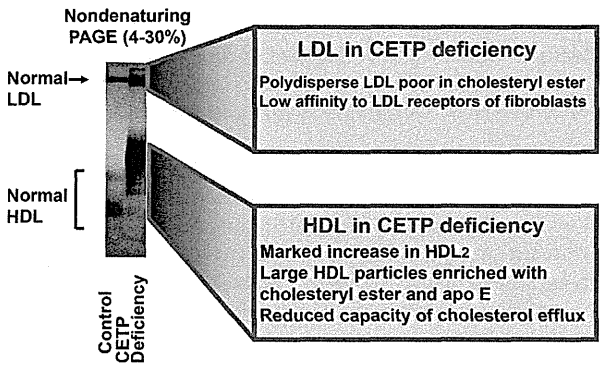

Figure 2 Lipoprotein Abnormalities of CETP Deficiency. The functions and composition of both LDL and HDL are abnormal in CETP deficiency. Thus, hyperalphalipoproteinemia due to CETP Deficiency is a disorder of reverse cholesterol transport system.

Familial cholesteryl ester transfer protein (CETP) deficiency

The most important and frequent cause of primary high HDL syndrome is CETP deficiency. In Japan, many patients with hyperalphalipoproteinemia due to CETP deficiency have been identified. Patients with homozygous CETP deficiency present with extremely high plasma HDL-C levels (three to six times normal levels). Plasma levels of apo A-I, A-II, C-III and E are also increased whereas plasma apo B and apo B-containing lipoproteins are a little decreased. As illustrated in Figure 2, both LDL and HDL from CETP-deficient homozygotes are markedly abnormal in terms of their biochemical compositions and biological functions. Their HDL particles are very large and enriched with cholesteryl ester and apo E. Their LDL particles are small, polydisperse, and enriched with TG and apo B. From the point of biological function, their LDL demonstrates a reduced affinity for LDL receptors of fibroblasts whereas their HDL has a reduced ability to mediate cholesterol efflux from lipid-laden macrophages, suggesting the atherogenicity of both LDL and HDL.

The first CETP gene mutation identified was an intron 14 splicing defect (*IN14*), which is a null mutation with a dominant effect on plasma CETP activity/mass and HDL-C levels. The second CETP gene mutation was the missense mutation in exon 15 (*D442:G*). These mutations are very common in the Japanese population. The effect of *D442:G* mutation on plasma lipoproteins is less severe than that of *IN14*. *D442:G* homozygotes show moderately increased HDL-C levels. In other countries, some genetic variations have been reported to affect CETP mass and HDL-C levels.

There have been controversies on the atherogenicity of CETP deficiency. We found a unique area (Omagari, Akita Prefecture, Japan) where the subjects with a marked hyperalphalipoproteinemia (HDL-C $\geq$ 100 mg dl^{-1}) due to the *IN14* mutation are very

frequent. A population-based study in this area indicated a U-shaped relationship between plasma HDL-C level and the incidence of ischemic electrocardiographic changes. In subjects with HDL-C <1.81 mmol l^{-1} (70 mg dl^{-1}), the incidence increased in proportion to the HDL-C levels. The frequency of the *IN14* CETP gene mutation was higher in patients with CHD than in control subjects. In subjects aged >80 years, the prevalence of both marked hyperalphalipoproteinemia and the *IN14* splicing defect was significantly lower than in the younger generation. Thus, a marked hyperalphalipoproteinemia caused by *IN14* CETP gene mutation does not represent a longevity syndrome, suggesting the importance of re-evaluation of the clinical significance and pathophysiology of a marked hyperalphalipoproteinemia.

The relationship between CETP gene mutations and CHD in Japanese American men in the Honolulu Heart Program cohort was evaluated. Men, most of whom had a *D442:G* mutation, showed an increased risk of CHD, but the atherogenic effect of CETP deficiency was observed in subjects with moderately increased HDL-C levels but not in subjects with a marked hyperalphalipoproteinemia. In the Framingham Heart Study, plasma CETP activity was measured in 1978 participants and on the average follow-up of 15 years, 320 participants experienced a first cardiovascular disease event (fatal or nonfatal coronary heart disease, cerebrovascular disease, peripheral vascular disease, or heart failure). In multivariable analyses, plasma CETP activity was related inversely to the incidence of cardiovascular disease events (hazard ratio for activity, at or above the median of 0.72; 95% CI, 0.57–0.90; P=0.004 [compared with below median]; hazard ratio per SD increment, 0.86; 95% CI, 0.76–0.97; P=0.01). These prospective data suggested that lower plasma CETP activity was associated with a greater cardiovascular disease risk. Similar data have been reported from the Ludwigshafen Risk and Cardiovascular Health (LURIC) study in Europe, in which low plasma CETP mass levels were associated with increased cardiovascular and all-cause mortality. In LURIC study, decreased cholesterol efflux capacity was shown in patients with low plasma CETP mass levels. Furthermore, the *post hoc* analyses of KAROLA study demonstrated a similar tendency in relations between low plasma CETP mass levels and cardiovascular and all-cause mortality. Thus, these studies challenge the rationale of pharmacological CETP inhibition.

Inhibiting CETP activity may raise HDL-C and decrease LDL-C levels. Thus, a number of CETP inhibitors have been developed. The initial clinical trial (ILLUMINATE Study) with a CETP inhibitor, torcetrapib, in combination with atorvastatin was prematurely terminated because of an increased cardiovascular event rate and mortality in torcetrapib-treated patients. RADIANCE1 and RADIANCE2 studies examining the effect of torcetrapib on carotid intima-media thickness in patients with familial hypercholesterolemia and mixed dyslipidemia, respectively, were also terminated. No beneficial effect of torcetrapib was observed on carotid intima-media thickness. ILLUSTRATE study also showed a small favorable effect for torcetrapib in the change in normalized atheroma volume, however there was no significant difference in the change in atheroma volume for the most diseased vessel segment, suggesting that torcetrapib may have no significant effect on the progression of coronary atherosclerosis. The lack of efficacy of torcetrapib may be related to the mechanism of action of this drug class or to molecule-specific adverse effects. Torcetrapib significantly increased blood pressure because of the increase in aldosterone levels.

Dalcetrapib is a CETP inhibitor which raises plasma HDL-C levels, but does not decrease plasma LDL-C. Dal-OUTCOMES study investigated the effect of dalcetrapib, at a dose of 600 mg daily, or placebo, in addition to the best available evidence-based care on the risk of recurrent cardiovascular events who had a recent acute coronary syndrome. The study was also terminated because dalcetrapib increased HDL-C levels, but did not reduce the risk of recurrent cardiovascular events. Studies on other CETP inhibitors such as anacetrapib and evacetrapib are still going on. However, a recent evidence suggests that CETP inhibitors form a complex between themselves, CETP and HDL particles, which might interfere with many physiological functions of HDL. Therefore, CETP inhibition is not a good target of HDL-modifying therapy.

In contrast to CETP inhibitors, an enhancement of RCT may be a promising strategy. A lipid-lowering drug, probucol, has a long history of clinical application with established efficacy and safety profiles. It is a potent antioxidant drug that has been in clinical use during the past few decades for the treatment and prevention of cardiovascular diseases. As mentioned above, probucol is a unique drug because it reduces plasma HDL-C levels, but attenuates xanthomas. Its mechanism of pharmacologic actions at the molecular level has recently been elucidated. HDL-C reduction by probucol is based upon the increase in plasma CETP activity and hepatic SR-BI expression, and may not be a 'side effect' but it most likely might reflect an acceleration. Probucol inhibits the oxidation of LDL and enhances the cholesterol efflux capacity and anti-oxidative function of HDL particles because it transforms HDL particles to cholesterol-poor small ones and it increases the expression of PON-1 on HDL. The molecular bases of the various anti-atherogenic effects of probucol are illustrated in Figure 3. Probucol could be reconsidered as an option at least in case statins, which are known to be effective for lowering LDL-C levels and CHD risk, are not effective. A marked CHD risk reduction has recently been reported in long-term probucol treatment of patients with heterozygous familial hypercholesterolemia FH as well as those after coronary revascularization. Therefore, there is more than enough reason to believe that this old drug has much more to offer than known so far.

Hepatic triglyceride lipase (HL) deficiency

HL plays a role in the conversion of IDL into LDL by its TG lipase activity. HL also has the function for the remodeling of large, TG-rich HDL particles into smaller ones by hydrolyzing TG of HDL. HL also enhances the hepatic uptake of HDL lipids. Several mutations have been reported in the human *HL* gene. Human HL deficiency is characterized by increased IDL-cholesterol levels as well as large and TG-rich HDL particles. Some patients with HL deficiency were reported to have premature atherosclerosis.

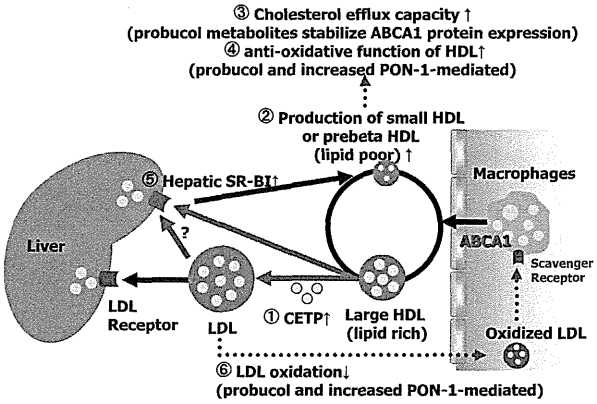

Figure 3 Molecular mechanisms for anti-atherogenic effects of probucol.

Familial hyperalphalipoproteinemia with premature corneal opacity (combined deficiency of CETP and HL activity)

Several patients with a combined reduction in CETP and HL activity were reported to present with corneal arcus and suffer from CHD. The impact of the combined reduction on atherosclerosis appears to be stronger than that of CETP deficiency alone. One of the possible mechanisms is that both CETP and HL play important roles in the remodeling of HDL particles from large to small particles, which are relatively more active for cholesterol efflux. The combined reduction of CETP and HL leads to the marked elevation of HDL-C, with the appearance of very large HDL particles, which are not active for cholesterol efflux.

Familial hyperalphalipoproteinemia with genetic abnormalities in SR-BI gene

Hepatic SR-BI takes up the cholesteryl ester from HDL particles. Adenovirus-mediated hepatic overexpression of SR-BI in mice resulted in virtual disappearance of plasma HDL and a substantial increase in biliary cholesterol. In contrast, the deletion of hepatic SR-BI increased plasma HDL-C, but enhanced the development and progression of atherosclerosis in mice.

From subjects with elevated HDL-C levels, a family with a new missense mutation (P297S) in the *SR-BI* gene has been identified. Cholesterol uptake from HDL by primary murine hepatocytes that expressed mutant SR-BI was reduced to half of that of hepatocytes expressing wild-type SR-BI. The P297S carriers showed increased HDL-C levels and a reduced capacity for cholesterol efflux from macrophages. However, the carotid artery intima-media thickness was similar in carriers and in family noncarriers. Platelets from carriers had increased unesterified cholesterol content and impaired function. In carriers, adrenal steroidogenesis was attenuated. Recently, two point mutations in human SR-BI gene, S112F or T175A, were also identified in subjects with high HDL-C levels.

Familial hyperalphalipoproteinemia with genetic abnormalities in EL gene

EL hydrolyzes the phospholipids of HDL. The gene of human EL is *LIPG*. Several genetic mutations or polymorphisms in the *LIPG* gene were reported. They show an increase in plasma HDL-C levels. However, recent a mendelian randomization study revealed that carriers of the *LIPG* Asn396Ser allele had higher HDL-C levels. However, the 396Ser allele was not associated with reduced risk of myocardial infarction. These data challenge the concept that raising of plasma HDL-C by inhibition of EL to reduce the risk of myocardial infarction.

Familial hyperalphalipoproteinemia with increased production of Apo A-I

A family with a marked hyperalphalipoproteinemia was reported to have an overproduction of apo A-I. The primary cause(s) is not known. We reported a hyperalphalipoproteinemic family with predominant increase in HDL_3. The cause of this hyperalphalipoproteinemia is speculated to be an increased production of apo A-I.

Familial hyperalphalipoproteinemia with reduced uptake of HDL by lymphocytes

A case of a marked hyperalphalipoproteinemia due to a reduced uptake of HDL by lymphocytes was reported. The molecular mechanisms for the reduction of HDL uptake by lymphocytes are unknown.

Secondary High HDL Syndrome

Chronic heavy alcohol consumption

Chronic heavy alcohol consumption is known to increase plasma HDL-C levels. Some enzymes and transfer proteins, such as CETP and HL, are altered in chronic heavy alcohol drinkers. CETP activity is reduced in these drinkers, but is normalized after cessation of

alcohol. The association between alcohol intake and mortality is U-shaped, suggesting that the beneficial effect of alcohol intake is only observed in mild to moderate drinkers.

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is a primary cholestatic liver disease, but its primary defect is unknown. In the end-stage of PBC, patients have very low HDL-C with the appearance of Lp-X, similar to other obstructive or cholestatic liver diseases. In the early stage of PBC, patients often demonstrate high HDL syndrome. In some cases, plasma HDL-C is markedly increased to the same extent as that in patients with CETP deficiency. In contrast to CETP deficiency, both activities and protein mass of CETP are markedly increased, whereas HL is reduced in patients with PBC.

Inhibitors of CETP in plasma

Defect in cholesteryl ester transport in serum of patients with uremia receiving maintenance hemodialysis was reported, suggesting an increased inhibitor activity against CETP in these patients.

Other factors or disease states accompanied by hyperalphalipoproteinemia

Aerobic exercise increases plasma HDL-C levels. Thus, hyperalphalipoproteinemia is sometimes observed in subjects who are continuously doing aerobic exercises. Patients with multiple symmetric lipomatosis, chronic obstructive pulmonary disease (COPD) and hypothyroidism are sometimes accompanied by hyperalphalipoproteinemia, but its mechanism is unknown except that HL activity is reduced in hypothyroidism.

Drugs

Some drugs, such as insulin, glucocorticoids, estrogen derivatives, fibrates, HMG-CoA reductase inhibitors (statins), nicotinic acids and their derivatives, intestinal cholesterol transporter inhibitor (ezetimibe), and cyclosporin were reported to increase plasma HDL-C levels. Prospective studies using a fibrate, gemfibrozil, demonstrated that increases in HDL-C during treatment were correlated with the prevention of cardiac events.

Conclusion

Various factors are involved in the etiology of low HDL syndrome and high HDL syndrome. A marked hyperalphalipoproteiemia caused by genetic CETP deficiency may not be protected from atherosclerotic cardiovascular diseases, therefore strategies to raise plasma HDL-C levels by CETP inhibitors have been challenged without a success. The enhancement of RCT by drugs such as probucol may have a greater potential as an anti-atherosclerotic treatment despite reduction of plasma HDL-C. The pleiotropic functions of HDL and efficiency of HDL-mediated RCT should be tested when we develop an HDL-targeted drug therapy for prevention of atherosclerosis.

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