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REVIEW

Current drugs, targets, and drug delivery systems for the treatment of dyslipidemia

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Abstract Cardiovascular diseases are the leading cause of death, and dyslipidemia is a significant risk factor for atherosclerotic cardiovascular disease. During the last several decades, development of drugs that reduce low density lipoprotein-cholesterol has been the focus in the treatment and prevention of dyslipidemia and cardiovascular diseases. In addition, statins and other cholesterol-reducing drugs have been the standard of treatment for dyslipidemia. Triglyceride (TG)-rich lipoproteins are also a significant risk factor for atherosclerosis and cardiovascular diseases, and pharmacological strategies to control TG-rich lipoproteins are now attracting much interest. In this review, mediators of lipoprotein metabolism and current therapeutic strategies with the formulation designs are discussed and new candidate therapeutic targets are presented.

Keywords Lipoprotein · Dyslipidemia · Cholesterol · Triglyceride · Drug delivery system

Introduction

Cardiovascular diseases including heart diseases and vascular diseases are the leading cause of death, and the global mortality rate has reached 29.2% according to the WHO report. Coronary arterial diseases are the most common heart disease, which are usually caused by the blockage of the vessels by atherosclerosis (Committee for the Korean Guidelines for the Management of Dyslipidemia 2015). Dyslipidemia is one of the major risk factors for atherosclerotic cardiovascular diseases along with hypertension, diabetes, and smoking. Other risk factors include obesity, low physical activity, stress, menopause, and genetic factors. High plasma low-density lipoprotein (LDL) cholesterol levels are regarded as the main cause and various drugs have been developed to reduce LDL-cholesterol levels (Rader et al. 2003). Especially, statins have significantly reduced cardiovascular incidences, suggesting that hypercholesterolemia is the most critical risk factor for atherosclerotic cardiovascular diseases, and treatment and prevention of hypercholesterolemia is essential to reduce the rates of cardiovascular diseases (Cholesterol 2005, 2012; Scandinavian Simvastatin Survival Study Group 1994). Recent epidemic studies and genetic studies have examined the roles of new aspects of dyslipidemia in atherosclerotic cardiovascular diseases. Metabolic pathways that affect serum lipoprotein levels are reviewed and current therapies and other molecules that are considered as targets for treatment are discussed in this review.

Synthesis of cholesterol and triglycerides in liver

Liver is the main organ that synthesizes, uptakes, and distributes cholesterol and triglycerides (TG). Cholesterol and fatty acids are derived from dietary fat or de novo synthesis in cells. The synthesis of cholesterol and fatty acids is mainly regulated by transcriptional control of the genes involved in the pathways. Sterol regulatory element binding protein (SREBP) isoforms, SREBP-1a, SREBP-1c, and SREBP-2, are the major transcription factors that regulate genes encoding enzymes for fatty acid and cholesterol

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synthesis. SREBP-1c and SREBP-2 are the isoforms expressed in adult tissues and their roles are restricted to their respective pathways; SREBP-1c preferentially regulates transcription of genes involved in fatty acid and TG synthesis while SREBP-2 preferentially regulates genes required for cholesterol synthesis. SREBPs are synthesized as inactive precursors that exist in the endoplasmic reticulum (ER) membrane via their two hydrophobic transmembrane-spanning segments connected by a short loop. The NH_2-terminal domain of SREBP is the transcription factor region that must be released by the action of two proteases present in the Golgi apparatus. SREBP cleavage activating protein (SCAP) is required in this process to escort SREBP from the ER to Golgi and also to sense sterol levels in the cell (Horton et al. 2002). Other players in the SREBP processing are INSIG1 and INSIG2, which are associated with SCAP. When cellular cholesterol contents are low, INSIGs dissociate from the SCAP–SREBP complex so that the SREBP–SCAP complex moves to the Golgi where the NH_2-terminal domain is released (Goldstein et al. 2006; Sun et al. 2005). The released NH_2-terminal domain moves to the nucleus where it works as a transcription factor that binds to sterol response elements (SREs) in the promoters of its target genes. Enzymes that catalyze the synthesis of fatty acids, triglycerides, and NADPH required for the fatty acid synthesis, such as ATP-citrate lyase (ACL), acetyl-CoA carboxylase, fatty acid synthase, elongation of very long chain fatty acids-like 6 (ELOVL6), stearoyl-CoA desaturase, glycerol-3-phosphate acyl transferase, malic enzyme, and glucose 6-phosphate dehydrogenase, are regulated by SREBP-1c. SREBP-2 preferentially activates genes responsible for cholesterol synthesis and uptake. Most of the cholesterol biosynthetic enzymes, including HMG-CoA synthase and HMG-CoA reductase, as well as LDL receptor and proprotein convertase subtilisin-kexin type 9 (PCSK9) that determines the plasma LDL-cholesterol level are directly regulated by SREBP-2 (Horton et al. 2002, 2003). The physiological importance of SREBPs and SCAP in the regulation of cholesterol and TG homeostasis has been demonstrated in transgenic *Srebp-1c* and -2 and *Scap* knockout mice (Horton et al. 1998; Matsuda et al. 2001; Shimano et al. 1996, 1997). A study inhibiting SCAP in the liver of hamsters by using siRNA suggested that SCAP could be a candidate therapeutic target for dyslipidemia (Moon et al. 2012).

Lipoprotein metabolism

Cholesterol and TG in the liver are packed into lipoproteins and secreted into the plasma so that dietary or endogenous cholesterol and TG are distributed to peripheral tissues. In lipoproteins, hydrophobic lipids such as TG and cholesteryl esters are located inside of the particles, while phospholipids, free cholesterol, and proteins surround them outside. Five major classes of lipoproteins exist in the plasma: chylomicrons, very low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), LDL, and high-density lipoproteins (HDLs), which are classified based on the density and the size of the particles. Each type of lipoprotein contains different apolipoproteins. Chylomicrons and VLDLs are TG-rich particles and the largest and least dense lipoproteins, while HDLs are the smallest and most dense type of lipoprotein. Chylomicrons and VLDLs transport mostly triglycerides, while LDL and HDL carry mostly cholesterol (Morita 2016; Rader et al. 2008) (Fig. 1).

Transport of dietary lipids (chylomicron metabolism)

Dietary fats are digested and absorbed in the small intestine. The TG and cholesteryl esters of dietary origin are assembled with phospholipids, free cholesterol, and apolipoprotein (apo) B-48 to form chylomicrons in enterocytes and are transported via the lymphatic system to the bloodstream. TG in chylomicrons are hydrolyzed by lipoprotein lipase (LPL) localized on the capillaries of tissues to release free fatty acids that are internalized by cells. Fatty acids in the cells are oxidized in the mitochondria to generate energies or are re-esterified to triglycerides for storage. ApoC-II and apoC-III in chylomicrons activate and inhibit LPL, respectively. As the chylomicrons release fatty acids, the particles progressively shrink in size and become chylomicron remnants that are removed by the liver (Cohen and Fisher 2013; Morita 2016; Rader et al. 2008).

Transport of hepatic lipids (VLDL metabolism)

Lipids in the liver are transported in the form of VLDL. VLDLs contain high contents of triglycerides, similar to chylomicrons, but contain apoB-100 instead of apoB-48. Hepatic TG, cholesteryl esters, phospholipids, and apoB are assembled into VLDLs through the action of microsomal TG transfer protein (MTP). VLDLs are released into the blood and the TG in VLDLs are hydrolyzed by LPL to release fatty acids. As they release fatty acids, VLDLs shrink in size and become IDLs (VLDL remnants). IDLs are either taken up by the liver through the LDL receptor or further digested by hepatic lipase to form LDL particles. LDLs contain mostly cholesterol and apoB-100. LDLs are removed by the LDL receptor in the liver (Cohen and Fisher 2013; Morita 2016; Rader et al. 2008).

Reverse cholesterol transport (HDL metabolism)

Cholesterol cannot be degraded to generate energy in the body. Instead, cholesterol in the liver is excreted as free cholesterol in the bile or is converted into bile acids in

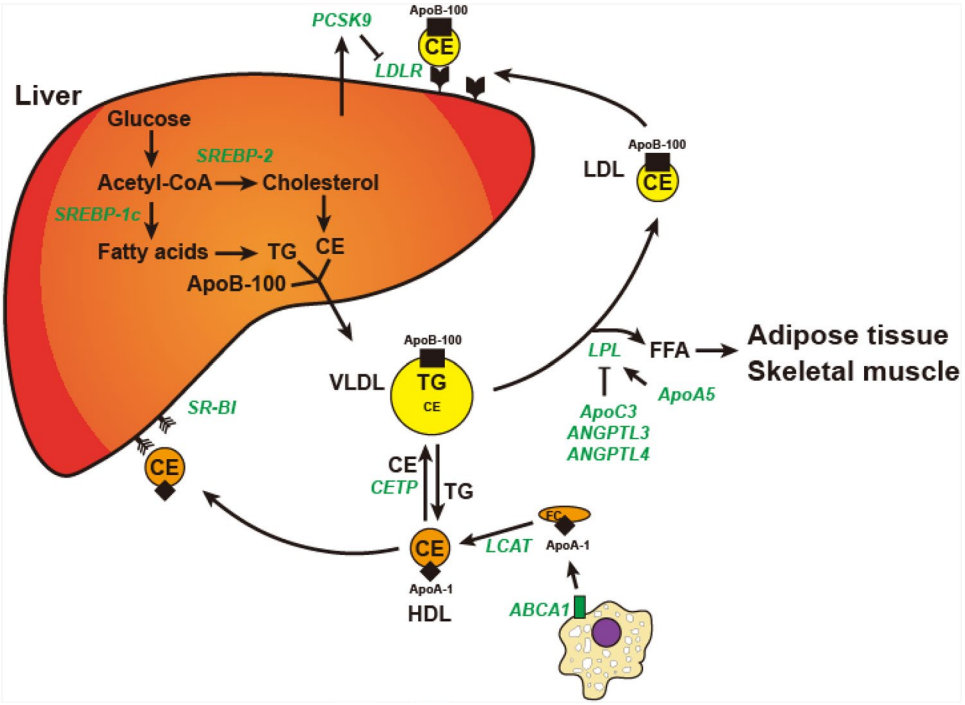

Fig. 1 Schematic of lipoprotein metabolic pathways and mediators. *ABCA1* ATP-binding cassette transporter A1, *ANGPTL* angiopoietin-like, *CETP* cholesteryl ester transfer protein, *LCAT* lecithin-cholesterol acyltransferase, *SR-BI* scavenger receptor class B member 1

hepatocytes, which are secreted into the intestinal lumen and excreted from the body as feces. Hepatocytes and enterocytes are the only cells that can excrete cholesterol from the body. Therefore, cholesterol shed from cells in other tissues needs to be transported to the liver, and this process is called reverse cholesterol transport. Nascent HDL particles are generated by assembly of apoA-I and phospholipids. ATP-binding cassette protein A1 (ABCA1) mediates the efflux of phospholipids and free cholesterol to apoA-I (Hobbs and Rader 1999). Free cholesterol from the peripheral cells is taken up by HDL particles and esterified by lecithin-cholesterol acyltransferase (LCAT) to generate cholesteryl esters within the HDL particle. Cholesterol ester transfer protein (CETP) in plasma transfers cholesteryl esters in HDL to VLDLs or LDLs that are taken up by LDLR. HDL-cholesterol is internalized via the cell surface receptor SR-BI (scavenger receptor class BI) in hepatocytes (Cohen and Fisher 2013; Morita 2016; Rader et al. 2008, 2009).

Therapies to control LDL-cholesterol

A strong correlation between serum LDL-cholesterol levels and the incidence of atherosclerosis and cardiovascular diseases has been demonstrated in various studies (Rader et al. 2003). Therefore, reducing LDL-cholesterol has been a major goal when treating dyslipidemia. One of the well-known human studies is from the homozygous familial hypercholesterolemia caused by a genetic mutation in the LDL receptor. A study of patients with homozygous familial hypercholesterolemia presented a clear correlation between high serum cholesterol levels in patients with atherosclerosis (Goldstein et al. 1973, 1983; Rader et al. 2003). PCSK9 lowers the protein level of LDL receptor. Recent studies have shown that individuals with a gain-of function mutation in PCSK9 exhibit high levels of LDL-cholesterol and a significant increase in cardiovascular disease risk. In contrast, individuals with hypomorphic mutations in PCSK9 have very low LDL-cholesterol levels and the mutations are associated with a substantial reduction in cardiovascular disease incidence (Abifadel et al. 2003; Cohen et al. 2005, 2006; Kotowski et al. 2006).

HMG-CoA reductase inhibitors (statins), cholesterol absorption inhibitors (ezetimibe), and bile acid sequestrants (resins) are currently used, alone or in combination, to treat hypercholesterolemia and have successfully reduced serum cholesterol levels (Bilheimer et al. 1983; Cannon et al. 2015; März et al. 2016; Lipid Research Clinics Program 1984; Scandinavian Simvastatin Survival Study Group 1994). Recently, PCSK9 monoclonal antibodies have been added to the list of drugs for hypercholesterolemia (Stein et al. 2012).

HMG-CoA reductase inhibitors (statins)

HMG-CoA reductase is the rate-limiting enzyme in the cholesterol biosynthesis pathway. Statins are inhibitors of HMG-CoA reductase that decrease the rate of cholesterol biosynthesis. Upon inhibition of cholesterol biosynthesis, hepatic LDL receptor activity is increased, thereby reducing serum LDL-cholesterol levels (Bilheimer et al. 1983;

Knopp 1999). Statins also reduce plasma TG in a dose-dependent manner, proportional to their LDL-cholesterol-lowering effects (Bakker-Arkema et al. 1996; Barter and Rye 2016; Garg and Grundy 1989; Kasim et al. 1992; Szapary and Rader 2001). Currently, new statins with better pharmacokinetic properties have been commercialized and are prevalent in the market (Table 1). Various drug delivery designs have been developed to minimize the drawbacks of each statin (Table 2).

Cholesterol absorption inhibitors

In the intestine, cholesterol, derived either from the diet or from bile, is absorbed by enterocytes, in a process mediated by Niemann-Pick C1-Like 1 (NPC1L1) (Altmann et al. 2004; Davis et al. 2004). Ezetimibe binds to NPC1L1 and prevents cholesterol absorption. Inhibition of intestinal cholesterol absorption eventually reduces cholesterol in the liver and increases LDL receptor activity. Ezetimibe possesses low solubility in aqueous solution. In order to enhance the dissolution rate of ezetimibe, various drug delivery systems, such as ordered mesoporous silica and solid dispersion techniques, have been developed and exhibited improved

Table 1 Pharmacokinetic parameters of statins (Kajinami et al. 2003)

Statins	Brand name	Dose (mg)	Lipophilicity (Log P)	BA[a] (%)	Metabolism	Protein binding (%)	$T_{2/1}$ (h)	Fecal excretion (%)
Atorvastatin	Lipitor Ator	10–80	4.06	12	CYP3A4	98	14	>98
Fluvastatin	Lescol Lescol XL	20–80	3.24	19–29	CYP2C9	>98	2.3	93
Lovastatin	Mevacor Altocor Altoprev	20	4.30	<5	CYP3A4	>95	2.9	83
Pitavastatin	Livalo Livazo	1–4	1.49	60	CYP2C9	96	12	79
Pravastatin	Selektine Pravachol Lipostat	5–40	−0.23	18	Non-CYP	50	1.3–2.8	70
Rosuvastatin	Crestor	5–80	−0.25	75	CYP2C9 CYP2C19	90	29	90
Simvastatin	Zocor Lipex	5–80	4.68	<5	CYP3A4	95–98	2.0–3.0	60

[a]*BA* bioavailability

Table 2 Pleiotropic effects of statins in various tissues via targeted drug delivery systems

Drug	Delivery design	Carriers	Outcomes/effects
Rosuvastatin	SNEDDS[a]	ω-3 Fatty acids	Improving drug solubility Anti-hypercholesterolemic effect (Abo Enin 2015)
Simvastatin	Microspheres and hydrogel	PLGA[b]/calcium phosphate	Bone tissue regeneration (Nath et al. 2014)
Simvastatin	Combination therapy	–	Anti-tumor activity (Licarete et al. 2015)
Simvastatin	Bioerodible devices	Cellulose acetate phthalate/pluronic F-127	Intermittent release of drug Stimulation of bone formation (Jeon et al. 2007)
Fluvastatin	Microspheres	PLGA[b]	Anti-inflammatory effect on osteoarthritis (Goto et al. 2017)
Lovastatin	Nanomatrix/lipid bilayer	Silicate/lipid	Sustained release of drug Improvement of oral absorption (Zhang et al. 2015)
Simvastatin	Aerosol	Inhaler	Anti-inflammatory effect on airway diseases (Xu et al. 2012)
Simvastatin	Lipid nanoparticles	High density lipoprotein	Anti-inflammatory effect on atherosclerotic plaque (Duivenvoorden et al. 2014)

[a]*SNEDDS* self nanoemulsifying drug delivery system

[b]*PLGA* poly(lactic-co-glycolic acid)

absorption in animal studies (Kiekens et al. 2012; Rashid et al. 2015). Ezetimibe is typically used in combination with a statin and is used in patients with stain intolerance (Barter and Rye 2016; Bruckert et al. 2003; Van Heek et al. 2001, 2003).

Bile acid sequestrants (resins)

Bile acid sequestrants, including cholestyramine, colestipol, and colesevelam, bind bile acids in the intestine and promote their excretion (Barter and Rye 2016; Knopp 1999). As the bile acid pool decreases, more cholesterol is converted to bile acids and the hepatic cholesterol content decreases.

PCSK9 monoclonal antibodies

PCSK9 secreted from the liver binds to the LDL receptors on hepatocytes and promotes the lysosomal degradation of these receptors (Grefhorst et al. 2008; Lagace et al. 2006). Therefore, plasma PCSK9 reduces LDL receptor levels, thereby reducing LDL uptake and degradation (Horton et al. 2009; Park et al. 2004). Various therapeutic antibodies against PCSK9 have been developed, which exhibited a dose-dependent reduction of serum LDL-cholesterol levels in clinical studies (phase 2 and phase 3), and their effects on cardiovascular disease incidence are under evaluation (Barter and Rye 2016; Kastelein et al. 2015; Roth et al. 2014; Stein et al. 2012). As an approach to inhibit PCSK9, RNAi has been introduced and studied in a non-human primate model and humans. These studies presented high effectiveness in reducing plasma PCSK9 and LDL-cholesterol levels as a result, which is in phase 2 clinical studies (Barter and Rye 2016; Fitzgerald et al. 2014, 2017; Frank-Kamenetsky et al. 2008). Efforts to develop small molecule inhibitors of PCSK9 are ongoing as well.

Treatment of the TG-HDL-axis

Nicotinic acid (niacin)

Nicotinic acid, also known as niacin or vitamin B3, was previously shown to reduce the flux of free fatty acids to the liver, thereby reducing hepatic TG synthesis and VLDL secretion. GPR109, a receptor for nicotinic acid, is expressed in adipocytes, where it suppresses the release of free fatty acids by adipose tissue (Tunaru et al. 2003). Niacin has been used for more than 50 years as a lipid-lowering drug that reduces plasma TG and LDL-cholesterol levels and raises the plasma HDL-cholesterol level (Creider et al. 2012; Ito 2015; Knopp 1999; Szapary and Rader 2001). In an effort to enhance the efficacy of niacin, products in extended-release forms, such as Slo-Niacin and Niaspan, have been developed and are currently available in the U.S. market. Extended-release niacin controls plasma lipid levels efficiently and seems safer, with fewer side effects on the liver and fewer hot flushes than the conventional, immediate-release niacin. The extended-release form of niacin was included in a combination product with statin, which was withdrawn from the U.S. market at the end of 2015 by the U.S. FDA because of its association with an elevated risk of serious side effects including muscle damage, kidney failure, and rhabdomyolysis (Table 3).

Fibrates (fibric acid derivatives)

Fibrates are PPARα (peroxisome-proliferator activated receptor) agonists that regulate carbohydrate and lipid metabolism. Fibrates stimulate LPL activity, reduce apoC-III, and may reduce VLDL production (Staels et al. 1997). Currently, fibrates are known as the most effective drugs to reduce TG levels and also raise HDL-cholesterol levels modestly (Ito 2015; Jun et al. 2010; Knopp 1999; Szapary and Rader 2001). Fibrates in various forms with different

Table 3 Combination drugs for the treatment of dyslipidemia with associated diseases

Drug combination	Brand name	Combination mode targets
Atorvastatin + Amlodipine	Caduet, Envacar	LDL-cholesterol, hypertension
Lovastatin + Niacin[a]	Advicor, Mevacor	LDL-cholesterol TG
Simvastatin + Ezetimibe	Vytorin, Inegy	LDL-cholesterol
Simvastatin + Niacin[a]	Simcor	LDL-cholesterol TG
Pitavastatin + Valsartan	Rovatitan	LDL-cholesterol, hypertension
Rosuvastatin + Telmisartan	Rostel	LDL-cholesterol, hypertension
Rosuvastatin + Olmesartan	Olostar	LDL-cholesterol, hypertension
Rosuvastatin + ω-3 Fatty Acids	–	LDL-cholesterol, TG

[a]Withdrawn by the U.S. FDA (2015)

pharmacokinetics and bio-availabilities are available on the market as Tricor, Lofibra, Lipofen, and Antara.

Omega 3 fatty acids (fish oils)

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the major ω-3 polyunsaturated fatty acids that play a role in human physiology and are found in high concentration in fish oil. ω-3 PUFAs inhibit SREBP-1c activity at the transcriptional and post-transcriptional level and reduce fatty acid synthesis (Jump et al. 2008). They are used in combination with fibrates, niacin, or statins to treat hypertriglyceridemia (Ito 2015; Szapary and Rader 2001).

ApoA-I

ApoA-I is an apolipoprotein for HDL. ApoA-I mimics have been developed to raise HDL-cholesterol level and to control dyslipidemia. Clinical trials with apoA-I have not been promising and recent human epidemiological and genetic studies have revealed that TG-rich lipoproteins have better correlations with cardiovascular diseases than low HDL-cholesterol level does (Tardif et al. 2007, 2014). However, strategies to enhance HDL-cholesterol are still being pursued.

Other approaches

There are patients who cannot tolerate any of the existing lipid-lowering drugs at doses normally required for adequate control of the lipid levels, and there are interindividual variations in drug efficiency. Therefore, new strategies for dyslipidemia targeting hypercholesterolemia or hypertriglyceridemia are being researched and discovered.

Previous population studies found that high levels of TG-rich lipoproteins are associated with low HDL-cholesterol levels, and that low HDL-cholesterol level has a better correlation with cardiovascular diseases than triglyceride level does (Assmann et al. 2002). Based on this study, low HDL-cholesterol level was recognized as a predictor of cardiovascular disease and strategies that raise HDL-cholesterol levels has been developed and studied, but the effects of raising HDL-cholesterol on cardiovascular risks remain unclear (Barter et al. 2007; Schwartz et al. 2012; The AIM-HIGH Investigators 2011; Voight et al. 2012). Recent epidemiological and genetic studies reveal that high levels of TG-rich lipoproteins, rather than low HDL-cholesterol level, are a risk factor associated with cardiovascular diseases. Therefore, strategies to control TG-rich lipoprotein are being developed and studied (Cullen 2000; Sarwar et al. 2007). Dyslipidemia is commonly associated with other metabolic diseases such as insulin resistance, obesity, fatty liver, and hypertension, which are also risk factors for cardiovascular diseases. Drugs to treat both dyslipidemia and other symptoms in combination would be beneficial for controlling metabolic disorders and cardiovascular events. Combination products that contain statins and hypertension drugs in one pill are becoming popular, and combinations of statins with TG reducing drugs are currently under development (Table 3).

Controlling LPL activity: inhibitors and activators

Recent large epidemiological and genetic studies have suggested that TG-rich lipoproteins are also causal factors for atherosclerosis and cardiovascular diseases. Common genetic variants associated with TG levels are significantly associated with cardiovascular diseases, even after controlling for the effects of LDL-cholesterol and HDL-cholesterol levels. An LPL variant (S447X), a gain of function mutation, presented significant association with lower TG levels and also a lower risk of cardiovascular diseases in prospective studies (Jensen et al. 2009). ApoC-III is an inhibitor of LPL activity that reduces TG lipolysis. Loss-of-function variants of apo-CIII are associated with reduced TG levels and reduced cardiovascular diseases, which makes apoC-III an attractive therapeutic target for hypertriglyceridemia (Jørgensen et al. 2014; Pollin et al. 2008; The TG HDL Working Group of the Exome Sequencing Project, National Heart, Lung, Blood Institute 2014). Targeting apoC-III in the liver with an antisense oligonucleotide targeting hepatic *APOC3* mRNA was studied in patients with dyslipidemia (phase 2), and was shown to reduce plasma TG by 30–70% (Gaudet et al. 2014, 2015).

Two other inhibitors of LPL are angiopoietin-like 3 (ANGPTL3) and ANGPTL4, which are circulating proteins. Genetic variants of both genes that are significantly associated with plasma TG levels were found, and both genes are considered as potential therapeutic targets for hypertriglyceridemia (Dijk and Kersten 2016; Mattijssen and Kersten 2012; Musunuru et al. 2010; Tikka and Jauhiainen 2016).

ApoA-V is an apolipoprotein associated with TG-rich lipoproteins, which promotes LPL activity through an unknown mechanism. There is a strong correlation between genetic variations in the *APOA5* gene with serum TG level and cardiovascular diseases (Do et al. 2015). ApoA-V mimics that enhance LPL activity could be a strategy to reduce serum TG levels. Strategies for pharmacological activation of LPL by using a small molecule could be developed for treatment of hypertriglyceridemia.

ACL inhibition

ACL is an enzyme that generates cytosolic acetyl-CoA, the substrate for cholesterol and fatty acid synthesis in the

liver. Liver-specific *ACL*-deficient mice were protected from hepatic steatosis and dyslipidemia, which suggested that ACL inhibition could be a therapy for dyslipidemia. An ACL inhibitor was developed and used in phase 2 clinical trials and showed an LDL-cholesterol lowering effect (Nikolic et al. 2014; Samsoondar et al. 2017).

Conclusions

During the last several decades, development of drugs to reduce LDL-cholesterol has been the focus for treatment and prevention of dyslipidemia and cardiovascular diseases. Statins have successfully reduced cardiovascular risks and are the standard treatment for dyslipidemia. Despite the promising effects seen in many patients, statin intolerance or resistance are observed in some patients. The recent development of PCSK9 inhibitors represents a new addition to the LDL-lowering treatment for individuals who cannot sufficiently reduce their LDL-cholesterol levels with statins. Recent human genetics studies and population studies have suggested that TG-rich lipoproteins are also a significant risk factor for the development of atherosclerosis and cardiovascular diseases. Pharmacological strategies to control TG-rich lipoproteins are now becoming of interest and new strategies are being pursued. Various molecules in metabolic pathways of cholesterol, fatty acids, bile acids, and lipoproteins have been extensively studied to identify new targeting molecules for dyslipidemia, but there exist many other potential molecules that could represent novel targets.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human and animal studies This article does not contain any studies with human and animal subjects performed by any of the authors.

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