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COMMENTARY

CREBH regulation of lipid metabolism through multifaceted functions that improve arteriosclerosis

Cyclic adenosine monophosphate (AMP)-responsive element-binding protein H (CREBH, encoded by CREB3L3), an endoplasmic reticulum membrane-bound transcription factor, is expressed only in the liver and small intestine. The overexpression of hepatic CREBH normalizes plasma glucose, and triglyceride levels are increased by high nutrient diets, such as a high-fat high-sucrose diet[1]. CREBH increases the expression of hepatic genes and the plasma levels of fibroblast growth factor 21 (*FGF21*), controlling systemic glucose and lipid metabolism[1–3]. *Fgf21* expression is also regulated by peroxisome proliferator-activated receptor α (PPARα). CREBH directly regulates hepatic *Fgf21* expression and indirectly regulates it through synergistic interaction with PPARα[1]. Additionally, CREBH directly increases the gene expression of apolipoproteins, such as apolipoprotein A4 (ApoA4), ApoA5, and ApoC2 in the liver, activating lipoprotein lipase (LPL) in the blood (Figure 1)[2,3]. These changes lead to reduced plasma triglyceride levels[1,4]. Thus, a CREBH deficiency causes abnormal lipid metabolism and exacerbates dyslipidemia[1,4]. Moreover, loss-of-function mutations in CREBH are associated with severe hypertriglyceridemia in humans[4]. With such reports, it could be assumed that CREBH affects the development of atherosclerosis, a lifestyle-related terminal disease. Indeed, the effects of CREBH on a mouse model of atherosclerosis have been reported[2,3]. Hepatic CREBH overexpression in low-density lipoprotein receptor (LDLR) knockout (KO) mice, an atherosclerosis mouse model, ameliorates atherosclerosis by normalizing plasma triglyceride levels[2]. The deficiency of CREBH in these mice exacerbates atherosclerosis[2,3]. However, the known mechanisms of CREBH can not explain all the effects of CREBH on atherosclerosis. A reduction in plasma triglyceride levels by CREBH activates LPL by controlling the gene expression of apolipoproteins. A deficiency of CREBH reduces plasma LPL activity in LDLR KO mice[3].

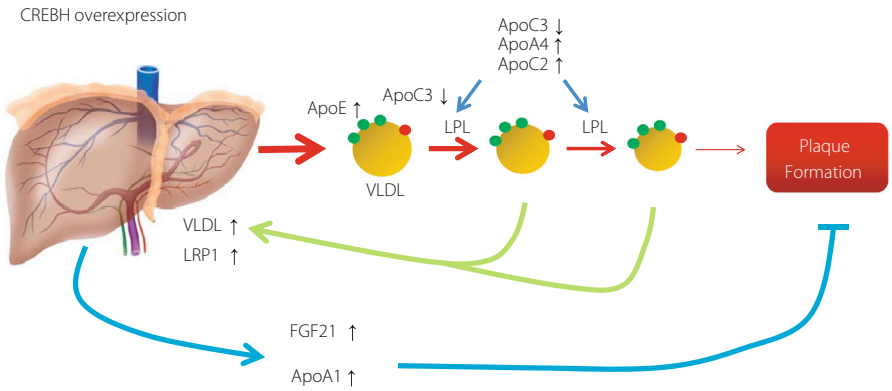

Figure 1 | Enhanced lipoprotein remnant clearance ameliorates atherosclerosis in mice ectopically expressing cyclic adenosine monophosphate-responsive element-binding protein H (CREBH). CREBH activates the lipoprotein lipase (LPL) activity by modulating apolipoproteins. Activated LPL hydrolyzes triglyceride-rich lipoproteins, such as very low-density lipoprotein (VLDL) and chylomicrons, producing remnant lipoproteins. CREBH increases apolipoprotein E (ApoE), a ligand that mediates the clearance of remnant particles and reduces ApoC3, which interferes with remnant clearance. CREBH also improves VLDL receptor (VLDLR) and LDL receptor-related protein 1 (LRP1) protein that mediates remnant clearance. Therefore, CREBH promotes the clearance of remnant particles from the blood, decreasing the atherogenic plaque area. CREBH induces the secretion of fibroblast growth factor 21 (FGF21) into the blood, decreasing plasma triglyceride. CREBH produces ApoA1 and then increases plasma HDL-cholesterol levels.

Lipoprotein lipase activity is closely associated with diabetes because it is mainly regulated by insulin. Therefore, diabetes increases the risk of arteriosclerosis by suppressing LPL activity as a result of insulin dysfunction. Diabetes mellitus comprises Type 1 and Type 2. There are higher levels of plasma insulin in Type 2 diabetes mellitus caused by insulin resistance owing to obesity. Type 1 diabetes mellitus is caused by insulin deficiency or insulin depletion; thus, in Type 1 diabetes mellitus there is a lower LPL activity than in Type 2 diabetes

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mellitus. Patients with Type 1 diabetes mellitus have increased plasma glucose and plasma lipids, including triglyceride and cholesterol compared with patients with nondiabetes. Additionally, plasma apolipoproteins levels, such as ApoE, ApoC2, and ApoC3, are also increased. As insulin inhibits *Apoc3* expression, hepatic *Apoc3* expression is elevated in patients with Type 1 diabetes mellitus. The increase in plasma ApoC3 levels inhibits plasma LPL-mediated lipolysis and the uptake of remnant-like particles into the liver, exacerbating dyslipidemia. Altogether, Type 1 diabetes mellitus indicates hyperlipidemia by lowering the uptake of triglyceride-rich lipoproteins (TRLs) into the liver. CREBH controls the gene expression of apolipoproteins, activating plasma LPL activity[1–4]. CREBH also increases lipid metabolism in a mouse model of Type 2 diabetes mellitus by the activation of LPL activity. However, the effects of CREBH on LPL activity in Type 1 diabetes mellitus remain unknown. Shimizu-Albergine *et al.*[5] revealed the impact of CREBH on LPL activity in diabetic atherosclerosis. LDLR KO mice were injected with lymphocytic choriomeningitis virus to generate a diabetic-atherosclerosis model (Type 1 diabetes mellitus atherogenic mice). CREBH was overexpressed in these mice by administering adeno-associated virus-CREBH. Consistent with previous reports[2–4], CREBH increased typical target genes, such as *Apoa4*, *Apoa5*, and *Apoc2*, even in these mice (Figure 1). However, CREBH did not improve LPL activity in postheparin plasma or tissues. Regarding the effect of CREBH on LPL activation, there are reports of activation and nonactivation but no conclusion has been drawn. Shimizu-Albergine *et al.*[5] evaluated the effects of CREBH in LPL KO mice. CREBH overexpression reduced plasma triglycerides and cholesterol even in LPL KO mice, revealing that CREBH could independently reduce them in the absence of LPL. Therefore, it can be assumed that there are mechanisms for reducing plasma lipids by CREBH other than LPL.

FGF21 enhances systemic lipid metabolism, so it may contribute to ameliorating atherosclerosis. A previous report indicated that administration of FGF21 to mice with atherosclerosis causes relief of this disease. CREBH induces *Fgf21* expression even in nondiabetic and diabetic LDLR KO mice (Figure 1)[2,3,5]. Thus, the improvement of atherosclerosis by CREBH overexpression is partly because of FGF21. However, CREBH overexpressing LDLR KO mice retain these effects even when FGF21 is deficient[2]. Thus, CREBH has LPL- and FGF21-independent mechanisms to alleviate atherosclerosis.

Shimizu-Albergine *et al.*[5] found for the first time that ApoE-mediated remnant clearance is essential for improving arteriosclerosis by CREBH. ApoE is a major apolipoprotein involved in lipoproteins, such as low-density lipoprotein (LDL) and high-density lipoprotein (HDL). ApoE serves as a major ligand for the uptake of chylomicron- and very low-density lipoprotein (VLDL) remnants into the hepatocytes through VLDL receptor (VLDLR), LDL receptor-related protein 1 (LRP1), and cell surface heparan sulfate proteoglycans. Therefore, mice with an ApoE deficiency (ApoE KO mice) have increased plasma lipoproteins and develop severe atherosclerosis. The levels of plasma ApoE are increased in diabetic mice, and are accompanied by a severe impairment of TRL clearance. Shimizu-Albergine *et al.*[5] showed that the expression of *Vldlr* and *Lrp1* was increased in CREBH overexpressing mice, increasing the hepatic uptake of TRL remnants by binding to ApoE on those particles (Figure 1). Other apolipoproteins, such as ApoC3, inhibit the clearance of TRLs and their remnants by interfering with the LDL receptor family. Overexpression of CREBH also inhibited *Apoc3* expression, improving lipid metabolism (Figure 1). These changes reduced the plasma lipid levels in CREBH-overexpressed mice in nondiabetic and diabetic mice. Shimizu-Albergine *et al.*[5] reported that overexpression of CREBH in ApoE KO mice reduced plasma triglyceride levels but not plasma cholesterol levels. Shimizu-Albergine *et al.*[5] showed that the reduction of plasma lipids by CREBH is because of residual TRL remnant clearance rather than because of LPL activation by modulating apolipoproteins.

Overexpression of CREBH increased *Apoe* expression in nondiabetic and diabetic mice with atherosclerosis[5]. However, it cannot verify whether CREBH directly regulates *Apoe* expression. CREBH interacts with other transcription factors, such as PPARα and sterol regulatory element-binding protein (SREBP) and regulates the function of transcription factors[1,2]. Previous reports showed that liver X receptor alpha (LXRα) regulates *Apoe* expression and CREBH associates with LXRα to modulate the expression of LXR target genes. Therefore, CREBH and LXR might cooperate in *Apoe* expression. However, since other reports show that CREBH overexpression cannot induce *Apoe* expression in the liver of nondiabetic mice with atherosclerosis [2,3], it is unclear whether CREBH regulates the expression of *Apoe*.

CREBH contributes to the metabolism of HDL. CREBH deficiency reduces plasma HDL-cholesterol levels in LDLR KO mice by reducing plasma ApoA1 levels[3]. Conversely, overexpression of CREBH increases hepatic ApoA1 levels, subsequently increasing plasma HDL-cholesterol levels (Figure 1)[3]. However, Shimizu-Albergine *et al.*[5] reported that CREBH does not change the content of HDL particles in nondiabetic and diabetic LDLR KO mice.

The analysis in mice has shown that CREBH affects lipid metabolism and contributes to the normalization of blood lipids. Thus, there is interest in the function of CREBH in human diseases. In fact, a few reports have shown that individuals with mutations of CREBH have hypertriglyceridemia[4]. Additionally, Shimizu-Albergine *et al.*[5] also analyzed CREBH function in humans. Consistent with their mouse study, Shimizu-Albergine *et al.*[5] showed that individuals with function loss and missense mutations in CREBH had hyperlipidemia with higher plasma triglyceride and cholesterol levels and lower plasma HDL-cholesterol levels. In

particular, these individuals had increased levels of remnants and decreased levels of ApoE in the VLDL + VLDL fraction. These patients had an increased accumulation of small remnants in the blood because of impaired hepatic TRL clearance. Additionally, these individuals had an increase in the larger size particles in the blood, which might be dependent on defects in LPL activity. However, there were no differences in the CREBH targets ApoC2 and ApoA4 or in ApoC3 between normal individuals and those with CREBH mutations[5].

CREBH normalizes lipid metabolism from its multifaceted effects by regulating different actions, such as the activation of fatty acid oxidation, the suppression of lipid synthesis, LPL activation, FGF21 elevation, and remnant metabolism. CREBH can enhance hyperlipidemia even in LPL KO or FGF21 KO mice[2,5]. Even if one mechanism is inhibited, it is compensated for by other functions. As a new mechanism, Shimizu-Albergine *et al.*[5] discovered that CREBH enhances hyperlipidemia and atherosclerosis in nondiabetes and diabetes by activating the uptake of TRLs. Shimizu-Albergine *et al.*[5] clarified that CREBH greatly contributes to remnant metabolism, lipid metabolism, and the normalization of arteriosclerosis. These findings provide new evidence that CREBH has beneficial effects on plasma lipid metabolism and would be a therapeutic target for dyslipidemia and atherosclerosis.

DISCLOSURE

The authors declare no conflict of interest.

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