

Angiotensin-like protein 3 and Cardiovascular Diseases: A Mini REVIEW

Abstract

This study is aimed at finding the association between the mutations and expressions of **Angiotensin-like protein 3 (ANGPTL3)**, LDL receptor and apoB100 as well as the association between gene mutations and lipid levels in type 2 diabetics. **The study also intends to study** whether silencing of ANGPTL3 gene in mice models reduces lipid levels and lowers the risk of **Cardiovascular Diseases (CVD)**. The effect of ANGPTL3 in regulating plasma lipid metabolism and thereby contributing to the risk of CVD in diabetes is the need for the hour. Cardiovascular disease is the most important cause of morbidity and mortality among patients with type 2 diabetes. ANGPTL3 therapies may have the potential to reinforce the current arsenal of lipid lowering agents, particularly for high-risk populations with refractory hyperlipidemia despite advanced treatments. Therapeutic application of ANGPTL3 gene editing could be of great value as it is independent of LDL receptor status. **The study** may acknowledge the important public health message of risk factor modification, in particular lipid lowering, for the prevention of **Coronary Heart Diseases (CHD)**. Additionally, because of the paucity of data and lack of well-designed studies that answer the questions on the efficacy, safety, and cost-effectiveness of long-term interventions to reduce LDL-C in high-risk populations.

Keywords: Angiotensin-like protein, Liver X receptor, Hyperlipidemia, ~~treatments~~

INTRODUCTION

Angiotensin-like protein 3 (ANGPTL3) is one of the major regulators of lipoprotein metabolism. It is specifically produced by the hepatocytes and then secreted into circulation. ANGPTL3 is regulated by liver X receptor (LXR), insulin and angiotensin-like protein 8 (ANGPTL8) [1, 2]. ANGPTL3 inhibits lipoprotein lipase as well endothelial lipase activity and therefore, increase serum triglyceride and HDL-c. Elevated plasma triacylglycerol (TG) and LDL-C levels are independent risk factors for CVD. There is an increase in the prevalence of diabetes being associated with the risk of Cardio-vascular disease. The effect of ANGPTL3 in regulating plasma lipid metabolism and thereby contributing to the risk of CVD in diabetes is the need for the hour.

Diabetes- Mellitus and Cardiovascular Diseases Risk

Cardiovascular disease is the most important cause of morbidity and mortality among patients with type 2 diabetes. Hyperglycemia, hypertension, even borderline-high-risk LDL cholesterol, and atherogenic dyslipidemia confers increased risk for CVD [3]. Over time, high blood glucose can damage the blood vessels and the nerves that control heart and blood vessels. Longer the duration of diabetes, higher the chances of developing heart disease [4]. In adults with diabetes, the most common causes of death are CVD and stroke. Risk of mortality due to CVD is double in diabetics as compared to non-diabetics [5].

Angiotensin-like protein 3 and Diabetes Mellitus

ANGPTL3 levels are associated with insulin sensitivity and glucose metabolism [6, 7]. High levels of hepatic ANGPTL3 mRNA and protein have been observed in insulin-resistant and insulin-deficient mice [7]. Insulin and ANGPTL3 may influence lipid metabolism and may predispose diabetics to a higher CVD risk.

Comment [D1]: Need some references to support idea

Angiotensin-like protein 3 and Cardiovascular Diseases

ANGPTL3 is an endogenous inhibitor of lipoprotein lipase (LPL). Rare loss-of-function variants in ANGPTL3 have been shown to be associated with decreased triglyceride levels as well as decreased low-density lipoprotein (LDL) cholesterol and High-Density lipoprotein (HDL) cholesterol levels. The disturbances in lipid metabolism, such as elevation of plasma LDL-C, TG and reduction of plasma HDL-C results in dyslipidemia and it is associated with CVD risk. Deficiency of ANGPTL3 is associated with hypolipidemia and reduced risk of CVD in Caucasians [8-10].

Comment [D2]: Need some references to support idea

Angiotensin-like protein 3 and Lipid profile

ANGPTL3 has been considered as an important and novel regulator of plasma lipids. By inhibiting Lipoprotein lipase (LPL) and endothelial lipase (EL) ANGPTL3 regulates plasma lipids. ANGPTL3 inactivation lowers LDL-C independently of the classical LDLR-mediated pathway. A study by Rene et al showed that ANGPTL3 inhibition reduces VLDL-lipid content and size, generating remnant particles that are efficiently removed from the circulation [11]. This suggests that ANGPTL3 inhibition lowers LDL-C by limiting LDL particle production.

Overexpression of ANGPTL3 and ANGPTL8 could both lead to increased serum TG levels in mice. On the contrary, in presence of loss of function mutations, the ability of ANGPTL3 to raise plasma TG levels decreased mildly [2].

Over the last few decades, tremendous progress has been made in understanding and decreasing the incidence of coronary heart disease (CHD). Low-density lipoprotein cholesterol (LDL-C) has been established as a major causal risk factor for atherosclerosis and CHD. Remarkable efforts have been made to develop LDL-lowering therapies, and statins have been proven to be an effective means of reducing the risk of CHD. However, even with the use of statin therapy, there remains a large residual risk of CHD, particularly in patients with familial hypercholesterolemia [12]. In light of these observations, an intensive search for new molecular targets to further reduce CHD risk is ongoing. Newer drug target is found to be proprotein convertase subtilisin/kexin type 9 (PCSK9) and it was confirmed to be useful with respect to the reduction of LDL-C levels in patients [13,14]. Since the efficacy of both statins and PCSK9 antibody therapies largely unclear [17] depends on functional LDL receptors, patients with LDL receptor deficiencies show limited responses to both therapies. In such circumstances, most appropriate promising molecular target is ANGPTL3.

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ANGPTL3 is unique in that it regulates all 3 major lipid traits: LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides. The primary action of ANGPTL3 is to inhibit lipoprotein lipase (LPL), which hydrolyzes the triglycerides carried in triglyceride rich lipoproteins in the circulation [15]. ANGPTL3 also inhibits endothelial lipase to modulate HDL-C metabolism [16]. The mechanism by which ANGPTL3 regulates LDL-C remains

Hence, the study is aimed at finding the association between the mutations and expressions of ANGPTL3, LDL receptor and apoB100 as well as the association between gene mutations and lipid levels in type 2 diabetics. The study also intends to study whether silencing of AGPTL3 gene in mice models reduces lipid levels and lowers the risk of CVD.

Comment [D4]: This sentence is not clear

ANGPTL3 therapies may have the potential to reinforce the current arsenal of lipid lowering agents, particularly for high-risk populations with refractory hyperlipidemia despite advanced treatments. Therapeutic application of ANGPTL3 gene editing could be of great value as it is independent of LDL receptor status. The aim of

this article is to suggest gene editing of ANGPTL3 would be beneficial in reducing CVD risk by lowering lipid levels in mice models.

Future Research Perspectives

A research study may be planned to find the association between mutations of ANGPTL3 and risk of CVD risk. This may emphasize the role of ANGPTL3 in predisposing diabetic patients to an added risk of CVD. Effectiveness of gene silencing of AGPTL3 in reducing lipid levels may be of great help in combating dyslipidemia of diabetes mellitus. There are no studies to the best of our knowledge which have combined human and animal experiments in a complementary manner as proposed.

Impact on the society

The study may acknowledge the important public health message of risk factor modification, in particular lipid lowering, for the prevention of CHD. The study emphasizes on the secondary prevention of CHD by focusing on the role of lipid lowering at the genetic level (that is, the treatment of low density lipoprotein (LDL) cholesterol) in delaying the progression of the clinical and angiographic findings in patients with clinically manifest CHD especially in diabetics. It is also importantly emphasizes that the unmet need for prevention and suitable treatment for diabetic and dislipidemic patients is likely to grow (with increasing numbers of such patients in the everyday clinical practice). Additionally, because of the paucity of data and lack of well-designed studies that answer the questions on the efficacy, safety, and cost-effectiveness of long-term interventions to reduce LDL-C in high-risk populations.

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Comment [D5]: Angioprotein

Comment [D6]: Old reference

Comment [D7]: Old reference

Comment [D8]: Complete data reference

Comment [D9]: Role of Writing reference

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