The role of angiopoietin-like 3 in the metabolism of lipoproteins: Therapeutic perspectives

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Abstract

Hyperlipidemia is at the cornerstone of cardiovascular disease development and progression. A number of treatment options are available for the management of increased cholesterol levels. However, some patients, especially those with familial hypercholesterolemia, do not achieve their low-density lipoprotein cholesterol target despite an aggressive treatment. Currently, the mainstay of hypolipemic treatment consists of statins, ezetimibe and more recently the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. However, novel hypolipidemic targets are constantly being researched and their efficacy and potential practical usage explored. Among them, the angiopoietin-like 3 (ANGPTL3) protein, by regulating a number of lipid homeostasis pathways as well as possibly having additional beneficial effects on carbohydrate homeostasis has piqued the interest of researchers and pharmaceutical companies. Moreover, it has been shown that loss-of-function mutations of the ANGPTL3 gene in subjects are associated with decreased cardiovascular risk without side effects. This lends credence to the hypothesis that targeting ANGPTL3 may be an attractive therapeutic option in the management of hyperlipidemia. The aim of this review is to depict the pathways in which ANGPTL3 is involved and consider the ways it could act as a therapeutic target for lipid and glucose homeostasis disorders.

Key words: angiopoietin-like 3 protein; hypercholesterolemia; cardiovascular disease; carbohydrate homeostasis

Citation

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Introduction

Familial hypobetalipoproteinemia is a hereditary disease of lipoprotein metabolism characterized by very low levels of low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B) [1]. The disease is genetically heterogeneous and may be attributed to mutations of the gene encoding ApoB resulting in reduced hepatic production of very low-density lipoprotein (VLDL) particles or mutations of the gene encoding angiopoietin-like 3 protein (ANGPTL3) [1]. The ANGPTL3 is a protein which is expressed predominantly in the liver, and inhibits the activity of lipoprotein lipase (LPL) and endothelial lipase (EL) [2]. Patients with mutations of this gene exhibit low levels of LDL-C, triglycerides (TRG) and high-density lipoprotein cholesterol (HDL-C) and as a result they present the phenotype of familial combined hypolipidemia (FHBL2) [3]. The resulting increase of LPL and EL activity explains the decrease of TRG and HDL-C, respectively, observed in these individuals. The decrease of LDL-C levels may be attributed to the effective catabolism of Apo B-containing lipoproteins, resulting in a reduced conversion of VLDL to LDL [4].

Available data on ANGPTL3 effects

Recent studies have shown that individuals with mutations of the Apo B gene have fatty liver disease and lower LDL-C levels compared with FHBL2 individuals who exhibit very low levels of HDL-C [5]. It should also be noted that ANGPTL3 may have an important role in carbohydrate homeostasis. Indeed, an experimental study has shown that the complete absence of this protein results in an increase in LPL activity, a decrease of free fatty acid (FFA) levels (due to the decrease of fatty acid mobilization from the adipose tissue) and an improvement of insulin sensitivity in peripheral tissues [4]. The decreased supply of fatty acids to the liver may explain the decrease in liver production of TRG-rich lipoproteins that was observed in some of these patients. The improvement of insulin sensitivity in the peripheral tissues is probably at least in part due to the decrease in FFA concentration (decrease of lipotoxicity) and is confirmed by a study which showed an increased incidence of ANGPTL3 gene mutations in subjects with low glucose levels [6].

Recent data highlight the importance of ANGPTL3 produced by hepatocytes in energy homeostasis of adipose tissue [7]. Normally during fasting adipose tissue releases fatty acids in systemic circulation that are taken up by tissues and serve as fuel. Moreover, after meals the release of FFA from adipose tissue is suppressed by insulin secretion, while fatty acids produced from LPL-induced TRG catabolism are acquired by the white adipose tissue (WAT). On the other hand, in ANGPTL3 deficient animals, fatty acid uptake by WAT is not increased after meals. This change in fatty acid uptake may be attributed to increased lipolysis of TRG in fatty acid oxidizing tissues such as muscles, heart and brown adipose tissue. However, despite this alteration in fatty acid uptake by WAT it was noticed that overall fat mass remained unchanged. Indeed, a 10-fold increase of glucose uptake into WAT and as a result increased de novo lipogenesis was utilized as an alternative countermeasure in order to preserve TRG depots. Therefore, this increased glucose consumption can additionally contribute to the improvement of glucose homeostasis in ANGPTL3 deficient animals. Thus, it appears that ANGPTL3 promotes the flow of fatty acids into WAT postprandially for the replenishment of TRG depots that decreased during fasting [2]. In the absence of ANGPTL3 there is a decrease in fatty tissue lipolysis during fasting and a decrease in plasma FFA levels (Fig. 1) [2].

Of interest, there is currently the capacity for a pharmaceutical intervention regarding ANGPTL3. Indeed, a recent randomized, placebo-controlled phase I study, evaluated: i) the effects of a monoclonal antibody against ANGPTL3 (evinacumab) in healthy volunteers with TRG levels between 150 and 450 mg/dL or LDL-C >100 mg/dL ii) the effects of evinacumab in atherosclerotic lesions on animals and iii) the risk for coronary artery disease in subjects with loss-of-function mutations of ANGPTL3 [8]. Treatment in healthy patients was well tolerated and resulted in a significant dose dependent decrease of TRG (up to 76%), LDL-C (up to 23%) and HDL-C (up to 18%) compared with subjects re-
Figure 1. Metabolic effects associated with the decrease of ANGPTL3 [Adapted from references [2, 14]]
Receiving placebo [8]. Treatment of animals resulted in decreased progression of atherosclerotic lesions with a reduction of their necrotic content [8]. Lastly, heterozygote subjects with loss-of-function mutations of ANGPTL3 had lower levels of TRG, LDL-C and HDL-C and lower incidence of coronary artery disease (relative risk 0.59, 95% Confidence Interval 0.41-0.85, p = 0.004) compared with controls [8].

Of note, another drug targeting ANGPTL3 and in particular an antisense oligonucleotide targeting the ANGPTL3 mRNA administered to 44 patients with increased TRG levels resulted in the dose-dependent reduction of ANGPTL3 levels by 46.6-85% [9]. Moreover, a dose-dependent decrease of LDL-C levels (1.3-32.9%), TRG (33.2-63.1%), non-HDL-C (10-36%), Apo B (3.4-25.7%) and Apo CIII (18.9% -58.8%) was observed. Treatment was also well tolerated. The study also evaluated the effects of this drug on mice and showed that in addition to improving lipid profile, drug administration reduced TRG deposition in the liver, decreased the progression of atherosclerotic lesions and increased peripheral tissue insulin sensitivity [9].

Lastly, in a small study, evinacumab was administered to 9 subjects with homozygous familial hypercholesterolemia [10]. The 4-week treatment period resulted in a reduction of LDL-C (by 49 ± 23%) with an absolute decrease of LDL-C levels by 157 ± 90 mg/dL, while decreasing levels of TRG [by 47% (interquartile range, 38 to 57)], HDL-C (by 36 ± 16%) and Apo B (by 46 ± 18%) [10]. These data suggest that ANGPTL3 might be an attractive therapeutic intervention for dyslipidemia after proprotein convertase subtilisin/kexin type 9 (PCSK9) [11, 12] (Table 1).

Another recent study has shown that 1/309 individuals in the general population are heterozygous for loss of function mutations of the ANGPTL3 gene [13]. These individuals had lower levels of TRG (by 17%) and LDL-C (by 12%) as well as decreased risk of developing cardiovascular disease by 34% (p=0.04). In addition, in the same study, subjects with the lowest tertile of circulating ANGPTL3 concentrations, compared with the highest, had 35% lower risk of developing cardiovascular disease (p<0.001). Moreover, the study identified 3 individuals with complete ANGPTL3 deficiency due to compound heterozygous loss-of-function ANGPTL3 and 3 matched first-degree relatives without loss-of-function ANGPTL3 mutation. The 3 compound heterozygotes did not exhibit atherosclerosis of the coronary arteries (as assessed by coronary calcium score), despite that one of these subjects had many cardiovascular risk factors (such as type 2 diabetes mellitus, hypertension and past tobacco use) [13]. On the other hand, 2 of 3 controls had positive coronary calcium score.

**Conclusions**

Drugs that decrease the activity of ANGPTL3 could be useful for the treatment of dyslipidemias (including familial hypercholesterolemia) in patients who do not achieve the treatment goals with currently available lipid-lowering drugs [14]. The improvement of insulin sensitivity is an added bene-

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<th>Table 1. Correlation of ANGPTL3 with atherosclerotic disease</th>
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<td>Experimental studies have shown that decreasing ANGPTL3 is associated with decreased progression of atherosclerotic disease</td>
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fit of these drugs. However, these drugs also reduce levels of HDL-C (due to a decrease of EL). Nevertheless, genetic studies do not confirm the association between HDL-C reduction and cardiovascular disease. Overall, ANGPTL3 may become a novel therapeutic target for several disorders of lipid metabolism, as well as impaired glucose homeostasis. Pharmaceutical agents aiming at reducing ANGPTL3 levels could potently improve cardiovascular outcomes and hopefully decrease cardiovascular morbidity and mortality.

Conflict of Interest
All authors declare no conflict of interest.