Apolipoprotein C-III - Summary

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1 Introduction

As the body of evidence grows for apoC-III's role in normal lipid homeostasis as well as its role in cardiovascular diseases, apoC-III is being put under the magnifying glass as a target for pharmacological therapy Li et al. [2014], Hernandez et al. [2010]. Studies first done on transgenic and knockout mice have given insights into the function of apoC-III. The over-expression of apoC-III in mice has resulted in severe hypertriglyceridemia Ito et al. [1990], while endogenous apoC-III deficiency decreases plasma triglycerides Maeda et al. [1994a]. The overall effects of apoC-III modulation in mice models are supported by genetic association studies in various human populations.van Dijk et al. [2004] High levels of apoC-III play a direct role in hypertriglyceridemia Jong et al. [1999], as hypertriglyceridemia is associated with metabolic syndrome, which in its self has a plethora of pathological consequences.

2 ApoC-III - Summary

The gene encoding apoC-III is located on the chromosome 11q23.3 Gray et al. [2012], The apoC-III gene is highly expressed by hepatocytes and by enteric cells. The final version of the expressed protein is a 79 amino-acid glycoprotein that is part of VLDL, chylomicrons, and HDL van Dijk et al. [2004].

2.1 Function

ApoC-III is synthesized chiefly in the liver and in small quantities by the intestines. ApoC-III appears to be the most abundant C apolipoprotein in human plasma at a concentration of $\approx$12 mg/dL, but this measurement was established by Nestel PJ [1982], a more up to date measurement needs to be obtained. ApoC-III predominantly affects VLDL-triglyceride metabolism which is a resultant of 3 variables: (1) increased intestinal triglyceride absorption, (2) increased VLDL - triglyceride production, and (3) disturbed lipolytic conversion of hepatic clearance of VLDL.

The two main properties of apoC-III are inhibition of lipolysis and displacement of apolipoproteins from lipoprotein particles. The displacement of apoC-II from lipoproteins would reduce apoC-II mediated activation of lipoprotein lipase (LPL), thus resulting in decrease catabolic rate of VLDL and chylomicrons and

progression to hypertriglyceridemia. Also, raised levels of apoC-III on the particle would displace apoE, a vital ligand for remnant removal, which would result in decreased remnant clearance and thus lipid overload.

Another role of apoC-III seems to be as a noncompetitive inhibitor or LPL Maeda et al. [1994b], An interesting discovery was made by Lins et al. [2002] that showed the 6-20 fragment of apoC-III is in a tilted peptide conformation, which is normally found only in viral fusogenic peptides (i.e. penetrating lipid bilayers), the structure of such a peptide seems to offer the potential flexibility to respond to its environment. From this van Dijk et al. [2004] offers the hypothesis that the apoC-III protein can adapt or perhaps sense its lipid or apolipoprotein context and that this mechanism presents apoC-III with the ability to dynamically regulate its function (i.e. the inhibition of LPL or hepatic remnant clearance) by changing its allosteric conformation.

A study done by Hernandez et al. [2010] concluded that peroxisome proliferator activated receptor γcoactivator 1-β (PPARγC1β) regulates plasma triglyceride metabolism through stimulating apoC-III expression thus elevating apoC-III circulating levels. The liver specific knockdown of apoC-III (in mice) significantly ameliorates PGC-1β-induced hypertriglyceridemia. The study also showed that PGC-1β or apoC-III knockdown in the liver recapitulates the hypolipidemic effect of nicotinic acid, thus denoting the importance of PGC-1β as an important regulator of the apoC-III gene, and it also reveals a mechanism via which nicotinic acid achieves its therapeutic effects.

2.2 ApoC-III - beneficial and detrimental mutations

The involvement apoC-III in cardiovascular pathology has been established using a genome-wide association study on Lancester Amish Pollin et al. [2008]. The study pinpointed that 5% of the population are heterozygous carriers of a null mutation (RX19) in the gene encoding apoC-III, as a result of this mutation they only express half of the circulating apoC-III present in non-carriers. Furthermore the mutation carriers had lower fasting and postprandial serum tryclicerides, higher levels of HDL-cholesterol and lower levels of LDL-cholesterol, the coronary artery calcification, was less common in carriers than in non-carriers, overall this would suggests that life-long deficiency of apoC-III has a pronounced cardioprotective effect.

Among the mutations that produce a protective status for the carrier of the mutation, scientific inquiry has revealed harmful mutations. Increased SstI RLFP (restriction fragment length polymorphism), localised to the apoC-III gene is associated with primary hypercholesterolemia, type III hyperlipoproteinemia, and with hypertriglyceridemia Henderson HE [1987].

Dammerman et al. [1993] detected in the promoter region a 5 DNA polymorphisms in the apoC-III gene in a subject with type III hyperlipidemia and sever hypertriglyceridemia. Experiments done on transgenic mice that overexpress plasma apoC-III have shown profiles of hypertriglyceridemia Li et al. [1995]. The study also correlated loss of insulin regulation, mapped to polymorphic sites at -482 and -455 (shown to be an insulin response element), with overex-

pression of apoC-III gene and development of hypertriglyceridemia. From this an hypothesis can be derived in which the overall insulin dysregulation in type I and complicated type II diabetes can promote a hypertriglyceridemic status and consequent cardiovascular complications. Variants of the insulin response element in the apoC-III gene promoter were shown to modulate insulin secretion and lipids load Waterworth et al. [2003]. The study employed the administration of oral glucose tolerance test (OGTT). Two variants of the insulin response element were evaluated (455T>C and 482C>T), the study's datum showed that the carriers of the specified variant alleles of the insulin response element had a disturbed glucose homeostasis and a unfavorable lipid load.

Another very interesting correlation was found by Oliviero Olivieri [2013] between the level of circulating apoC-III and the coagulation pathway, in subject with or without coronary artery disease. The study employed 933 subjects among which 687 were diagnosed angiographically with coronary artery disease (CAD) while 246 were CAD free, also the 687 were not taking anticoagulant drugs. The plasma activities of factor II (FII:c), factor V (FV:c), and factor VIII (FVIII:c), and activated factor VII (FVIIa) were analyzed. Subjects with >12.6mg d/L of circulating apoC-III had high levels of FII:c statistically similar of carriers of 20210A allele. The presence of high apoC-III combined with high thrombin activity could be accounted for high levels of cardiovascular incidents caused by thrombi formation in cardiovascular diseased subjects with hyperlipidemia.

The newest study done on apoC-III showed Cohorts [2014], that an aggregate of rare mutations in the gene encoding apoC-III was associated with lower plasma triglyceride levels. Among the four mutations that drove this result, three were loss-of-function mutations: a nonsense mutation (R19X) and two splice-site mutations (IVS2+1GA and IVS3+1GT). The fourth was a missense mutation (A43T). The triglycerides levels in the carriers of one mutation at least, were 39% lower than levels in non-carriers. The risk of coronary heart disease among 498 carriers of any rare apoC-III mutation was 46% lower than the risk among 110,472 non-carriers.

3 Conclusions

As the majority of scientific articles concluded, the importance that apoC-III plays in cardiovascular pathologies, coupled with metabolic dyshomeostasis makes the apolipoprotein a important target to consider in future pharmaceutical development. The success of mimicking a beneficial mutation, thus lowering the apoC-III levels or producing an inactive form of the protein, can bring tremendous burden release from cardiovascular diseases in a western society that is increasingly weighted down by this type of pathology.

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