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NEWS AND COMMENTARY

Apo E and hyperlipidemia type III

Unraveling hyperlipidemia type III (dysbetalipoproteinemia), slowly

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The expression of type III hyperlipidemia (HLP) is the topic of the paper by Peter Henneman and his colleagues.[1] Only very few lipid disorders seem to be more complex and poorly understood than the type III HLP by Fredrickson (or so-called dysbetalipoproteinemia). This is true despite the fact that type III HLP had been described in great detail more than 33 years ago[2] and since then had been studied intensively by the most dedicated, leading lipid researchers worldwide. Type III HLP is a genetic disorder characterized by the accumulation of remnant lipoproteins in the plasma and development of premature atherosclerosis.

In 1977, Utermann with his co-workers Hees and Steinmetz[3] identified in Marburg, Germany the rare form of apolipoprotein (apo) E 2/2 to be a crucial factor for the development of dysbetalipoproteinemia in humans. By this they identified apo E 2/2 to be the primary molecular cause of type III HLP.

Apo E is a fascinating structure and depending on the individual defect the consequences of a variation in apo E might cause hyperlipidemia, atherosclerosis or Alzheimer's disease. The apo E gene is located on chromosome 19q13.2 within a cluster with apo C-I and apo C-II. Apo E is produced in most organs with significant amounts in the liver, brain, spleen, lung, adrenal, ovary, kidney and muscle. Apo E is crucial for the metabolism of triglyceride-rich particles such as chylomicron remnants and very low-density lipoprotein (VLDL) remnants and constitutes up to 20% of the protein content of VLDL (and about 2% of that of the HDL). To some extent, apo E is able to replace *in vivo* a dysfunctional apo B-100 as in familial defective apo B (FDB). The triglyceride-rich particles were modified by the interaction with lipases, and were finally removed from the circulation by receptor-mediated endocytosis in the liver mostly by the LDL receptor or in adipose tissue or muscle by receptors such as the VLDL receptor. There are three different apo E alleles: apo E-2, which has two cysteine residues, one at position 112 and another at position 158; the most common (in Caucasians 60–80%) apo E-3 allele has only one cysteine at position 112 and an arginine at position 158; and apo E-4 allele, which has two arginine but no cysteine residues at positions 112 and 158. Apo E-2 has reduced binding affinities compared with apo E-3. In contrast, apo E-4 has a higher affinity for the LDL receptor. Interestingly, individuals with the apo E-4 variant are at higher risk for both, CAD as well as the early onset of Alzheimer's disease, indicating the amazingly broad role of apo E for the *in vivo* metabolism of lipoproteins.

Apo E is essential for the normal catabolism of triglyceride-rich lipoproteins and defects in apo E causes hypertriglyceridemia or type III HLP. Type III HLP in patients with apo E 2/2 is usually defined as an increase of the VLDL-cholesterol/triglyceride ratio to >0.3 and usually goes along with both – elevated total cholesterol as well as triglycerides. Patients with type III HLP have sometimes – but not always – xanthomas and/or yellowish lipid deposits in the palmar crease. Overt hyperlipidemia requires homozygosity for apo E-2. However, even in apo E-2 homozygotes only 10% will develop hyperlipidemia, thus leaving most of the apo E 2/2 patients either normolipidemic or even hypocholesterolemic. The mechanisms leading to hypocholesterolemia are currently poorly understood and there are at least three hypotheses trying to explain this effect of apo E-2. The defective binding of apo E-2-containing lipoproteins to the LDL receptors might cause an upregulation of hepatic LDL receptors and by this decrease the LDL cholesterol levels. Another hypothesis sees the poor competition between defective apo E-2-containing remnants and apo B-100-containing LDL for the hepatic LDL receptors. This could lead to an enhanced clearance of the LDL. Last but not least, apo E-2 might impair the lipolytic conversion of VLDL to LDL, leading to lower than normal LDL concentrations in apo E-2 patients. As one might expect, the normo- or even hypolipidemic apo E 2/2 patients have no increased risk for CAD. Additional genetic, hormonal, or other factors, such as drug effects, renal impairment, obesity, hypothyroidism, estrogen status, or diabetes, are required to serve as 'cofactors' to develop HLP III in apo E 2/2. By this, defective apo E (commonly apo E-2) is essential but not sufficient to cause overt type III HLP.

An enormous effort has been made to identify potential genetic cofactors causing type III HLP in apo E 2/2 patients. An extremely interesting candidate gene to serve as a crucial cofactor for the development of type III HLP was thought to be a defect of the apo A5. In some smaller studies apo A5 S19W, a mutant form of apo A5, was found in apo E 2/2 patients to cause hypertriglyceridemia or type III HLP, respectively.[4,5] In addition, apo A5 S19W is found at the same frequency in the general population as type III HLP occurs in apo E 2/2 patients (roughly 10%). It was intriguing to see apo A5 S19W as a potential cofactor for the development of HLP III. To clarify these observations and also to identify other cofactors of the lipolytic cascade in human lipoprotein metabolism it was necessary to set up a large-scale study in type III HLP apo E 2/2 patients. This extremely challenging project has now been undertaken by Peter

Henneman and his colleagues with their paper entitled 'The expression of type III hyperlipoproteinemia: involvement of lipolysis genes'.[1]

Henneman *et al*[1] studied for known genetic variants of various lipolysis genes and their contribution to the expression of type III HLP in a total of 165 apo E 2/2 patients. Of these patients, 113 were hyperlipidemic and 52 were normolipidemic. They tested for different polymorphisms in the apo C3, apo A5, hepatic lipase (HL) and lipoprotein lipase (LPL) genes. In addition, they studied 188 normolipidemic controls and 141 hypertriglyceridemic patients. They found that the frequency of the rare allele of APOC3 3238 G>C and APOA5 −1131 T>C was significantly higher in type III HLP patients compared with normolipidemic apo E 2/2 patients. Moreover, in the carriers of these polymorphisms the hyperlipidemia was more severe. 58% of the type III HLP patients carried either the APOC3 3238 G>C/APOA5 −1131 T>C polymorphism, APOA5 c.56 G>C and/or the LPL c.27 G>A mutation (as compared with 27% of the normolipidemic APOE2/2 patients). In summary, they found that the APOC3 3238 G>C, APOA5 −1131 T>C and to a lesser extent the LPL c.27 G>A mutation were associated with a more severe hyperlipidemia in type III patients, whereas the APOA5 c.56 G>C seemed to be a rather weak modifier. These results are clearly only part of a rather complex story and are in some conflict with earlier findings (ie, the role of LPL) in other populations.[6]

What does this carefully performed study tell us? Well, first of all type III HLP still keeps most of its secrets despite another major effort to unravel the mechanisms of this disease. Interestingly, most of the relevant polymorphisms such as APOC3 3238 G>C or the APOA5 −1131 T>C are located in the untranslated regions of APOC3 and APOA5, respectively and the mode of action of these polymorphisms is currently unclear. There could be an influence on mRNA stability or other mutations could be near to these polymorphic sites. Second, it becomes evident that the mechanisms can only be clarified by screening large and unrelated study populations and that a hypothesis driven, physiological target-tracking approach by analyzing part of the key players of the lipolytic system might not be sufficient in such a multifactorial disease. Clearly, a 'European wide apo E registry' is very much needed to study the mysteries of type III HLP in a genome-wide screening approach in more detail to understand the complexity of this disease, not only for the sake of atherosclerosis research but also for neurodegenerative mechanisms in which apo E plays an important role■

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