Cholesteryl Ester Transfer Protein: The Key to Longevity?

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The negative attributes of cholesterol receive much attention in the media and scientific literature, with good reason. However, there are aspects of cholesterol metabolism that actually reduce the risk of developing cardiovascular disease. Furthermore, variations in the gene for an important cholesterol transport protein may yield significant health benefits. This critical review outlines the basic physiology of cholesterol, discusses cholesteryl ester transfer protein and potential variations in its gene, and identifies the implications of current research in this field for the pharmaceutical industry.

During the past 25 years, the field of genetic research has advanced greatly. Whole genomes of organisms ranging from small viruses to complex human beings have been sequenced. Since the completion of the human genome project in 2003, breakthroughs in sequencing technology have allowed for genetic screening of certain diseases. Genetic screens can predict how likely an individual or their offspring are to develop certain diseases. Conversely, genetic screening can also determine the presence of beneficial genetic traits that may confer protection against developing certain diseases. This paper will elucidate how mutations in the cholesteryl ester transfer protein (CETP) gene confers a reduced risk of arterial and cognitive diseases.1,2

**BACKGROUND PHYSIOLOGY**

Cholesterol is a steroid metabolite, responsible for maintaining animal cell membrane permeability and structure. It is vital in the production of steroid hormones, bile acids, and some lipid-soluble vitamins.3 While the right amount of cholesterol is beneficial, research has shown that high levels are pathogenic.4

Cholesterol is mainly produced in the liver, intestines, adrenal glands, and reproductive organs. Given its hydrophobic property, lipoproteins assist in the transport of cholesterol in the blood plasma.5 In the liver, cholesterol is combined with apolipoproteins to form very low density lipoproteins (VLDL). Once it is released into the bloodstream, cholesterol is converted to low density lipoproteins (LDL) as it is deposited into various organs. However, LDL-cholesterol can be retained in arteries, leading to the formation of atherosclerotic plaques, which are implicated in causing peripheral vascular disease, strokes, and myocardial infarctions.4

In contrast, high density lipoprotein (HDL), or “good cholesterol”, removes cholesterol from arteries and transports them back to the liver for excretion or reuse.4 Epidemiological studies have shown LDL-cholesterol levels correlate positively with incidence of vascular diseases, while HDL-cholesterol levels inversely correlate with incidence of vascular diseases.6

Cholesterol metabolism is controlled by enzymes, membrane receptors, and transfer proteins in the gastrointestinal system and blood plasma. One particular cholesterol-regulating transfer protein that has been extensively studied is CETP.8 CETP is highly expressed in the liver, heart, placenta, and lymph nodes.7 The protein transports cholesteryl esters and triglycerides between VLDL, LDL and HDL.8 The net effect of CETP is a reduction in the content and size of HDL particles.4 Consequently, inhibition of CETP raises HDL-cholesterol levels and lowers LDL-cholesterol levels in the body. Since higher concentrations of HDL-cholesterol and lower concentrations of LDL-cholesterol are preventative against cardiovascular disease, drugs which inhibit CETP are being tested.4
CETP ALLELES AND POLYMORPHISMS

The CETP gene is located on chromosome 16 and contains a large variety of mutations that are highly polymorphic. Many of the mutations in the gene can be separated into three major groups including missense, nonsense and silent mutations. Missense mutations result in the production of single amino acid substitutions. These mutations are often milder, but some variants can have a significant effect on protein function. Nonsense mutations produce premature stop codons, causing the protein product to be prematurely truncated. This leads to either partial or complete CETP deficiency. Silent mutations do not produce an amino acid substitution due to the redundant nature of the genetic code. As a result they are thought to play only a minor role in CETP function.

A common missense mutation that causes partial CETP deficiency is the D442G variant, where aspartic acid at position 442 is substituted with a glycine. Heterozygotes for this allele retain 60-85% of normal CETP function. Being heterozygous for the D442G genotype has been associated with decreased risk for Alzheimer’s disease. Although there was no statistical significance, further adjustment of the data for sex and age showed that the G allele might be protective against the development of Alzheimer’s disease (corrected for multiple testing). This conclusion is supported by observations that the variants have altered CETP structure and function leading not only to reduced CETP levels, but lowered CETP activity in comparison to the wild type. Studies on heterozygotes showed that plasma CETP activity was only 60%-85% and HDL levels were elevated by 10%-80% in comparison to the wild type.

The I405V variant is the second most common variant found in over 25% of studied populations. Studies indicate that it is three times greater in the centenarian population than in people with a median age of 70. It is believed that individuals with the heterozygous genotype tend to produce both versions of CETP, as the alleles are co-dominant to one another. While both homozygous I/I and the heterozygous individuals produce almost identical amounts of CETP, the V/V homozygotes tend to have a 9-23% CETP deficiency. A decrease in CETP function increases HDL (high density lipoproteins) levels in the body, and decreases LDL (low density lipoprotein). The result of this is that HDL-c levels are approximately equal in individuals with the I/I or I/V genotypes, while they are ten percent higher in V/V individuals.

Not only do I405V V/V homozygotes tend to have higher HDL levels and low LDL levels, they produce larger HDL and LDL particles, which are less likely to get trapped in vessels. This results in a decreased risk of coronary artery disease or atherosclerosis. Furthermore, it is believed that lipid metabolism partially mediates the conservation of cognitive function in the brain, and as a result I405V variants tend to have reduced risk and onset of dementia as they age. 158 Ashkenazi Jews between 95 and 107 years of age were evaluated for cognitive function and tested for the CETP I405V variants. It was found that those with the CETP I405V genotype were twice as likely to have good cognitive function (a score greater than 25 on the Mini-Mental State Examination).

PHARMACOLOGICAL IMPLICATIONS

Recognizing the therapeutic potential of CETP inhibition, pharmaceutical companies have engineered and tested CETP inhibitors in clinical trials. Two prominent CETP inhibitors developed over the past decade are torcetrapib (engineered by Pfizer) and anacetrapib (engineered by Merck).
A 2004 study with a small sample size in the New England Journal of Medicine showed that Torcetrapib significantly increased HDL-cholesterol and decreased LDL-cholesterol levels. The effect was even greater when the drug was combined with statin therapy. However, ILLUMINATE, a subsequent study including 15,000 patients, indicated that while torcetrapib plus statin therapy raised HDL-cholesterol levels, compared to statin monotherapy this combination therapy caused an excess number of adverse events such as death and myocardial infarction. A further study, the ILLUSTRATE study, showed no difference in atherosclerotic plaque levels in the torcetrapib-statin combination therapy and the statin monotherapy groups. This indicates that torcetrapib causes adverse cardiovascular events by mechanisms other than atherosclerosis, such as vasospasm or potential interaction with the renin-angiotensin-aldosterone system. Due to its harmful effects, torcetrapib is no longer in development.

Anacetrapib on the other hand is still under development. Recent studies in The Lancet indicate that this drug has great potential. In healthy patients and patients with dyslipidemia it was shown to increase HDL-cholesterol and decrease LDL-cholesterol levels. Additionally, unlike torcetrapib it did not exhibit any off-target effects such as hypertension. Importantly, it also did not increase the incidence of adverse events. However, these are small phase 1 trials, and long-term safety and efficacy data for anacetrapib have not yet been reported.

Reviewed by Dr. Geoff Werstuck, Ph.D.
Dr. Geoff Werstuck is an Associate Professor at McMaster University in the Department of Medicine. His work at Henderson involves researching the molecular mechanisms by which diabetes mellitus promotes the progression and development of cardiovascular disease. His laboratory employs a broad range of molecular and cellular techniques to examine cell and tissue-specific responses to hyperglycemia. This includes identifying changes in atherosclerotic gene expression induced by hyperglycemia and determining the mechanisms of accelerated atherosclerosis in diabetic mouse models and human blood samples. His laboratory is especially interested in identifying and testing potential new targets for therapeutic intervention in the treatment and prevention of atherothrombotic cardiovascular disease.

REFERENCES

12 Tall AR. (2007). CETP Inhibitors to increase HDL cholesterol levels. NEJM, 356(13), 1364-1366.