Researchers identify structure of apolipoprotein

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Using a sophisticated technique of x-ray crystallography, researchers Xiaohu Mei, PhD, and David Atkinson, PhD, from Boston University School of Medicine (BUSM) have for the first time obtained an "image" of the structure and the precise arrangement of the atoms in a truncated form of the apolipoprotein A-I (apoA-I) molecule. The findings, which appear in the November issue of the *Journal of Biological Chemistry*, may lead to the development of new drugs to treat obesity, stroke and diabetes.

Errors in the regulation of the metabolism and transport of fats in the body are the number one cause of death and morbidity in the United States and most parts of the world. These problems are exemplified by the prevalence of diseases such as atherosclerosis, cardiovascular disease and stroke.

High blood levels of HDL or "good cholesterol" protect against atherosclerosis and cardiovascular disease. This protection is related HDL's role to remove cholesterol from cells in the tissues of the body. The major protein of HDL is called apoA-I. ApoA-I solubilizes fats and cholesterol and builds the HDL particle. ApoA-I plays important roles in the process of cholesterol removal by HDL.

ApoA-I interacts with another protein in the membrane of cells called the ABCA1 transporter, and removes cholesterol from the cells to form a "nascent" HDL particle.

In the blood, apoA-I in the nascent HDL activates the enzyme, lecithin-cholesterol acyltransferase (LCAT), which results in the solubilization of more cholesterol and the formation of a "mature" HDL particle. This HDL particle is transported in the blood stream to the liver where apoA-I binds to yet another cell membrane protein (hepatic SR-B1 receptor) and cholesterol is delivered to the liver and can be excreted from the body.

"Despite this central role in fat and cholesterol transport and metabolism, a detailed molecular understanding of apoA-I and how apoA-I forms an HDL particle have remained enigmatic for more than three decades," said study author David Atkinson, PhD, chairman and professor of physiology and Biophysics at BUSM as well as a research professor of biochemistry.

"The structure shows the precise molecular and atomic details of how two molecules of apoA-I bind to each other to form a half circle arrangement that can solubilize fatty molecules and cholesterol to form the "nascent" HDL. In addition, the structure suggests how a central section of the protein may form a tunnel through which cholesterol can be moved during the interaction with LCAT. Finally, the structure provides the molecular details that may underlie the structural and functional effects of important apoA-I mutations that cause abnormalities in HDL function," he explained.

According to the researcher, understanding, in molecular detail, the processes of fat and cholesterol transport, cellular uptake and removal is crucial to understanding how these processes occur in the healthy state and become dysregulated in diseases such as atherosclerosis. "With the mechanistic insights provided by this knowledge, new drugs may be developed to regulate and treat human diseases including obesity, atherosclerosis, stroke metabolic syndrome and the dyslipidemia associated with diabetes," added Atkinson.

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