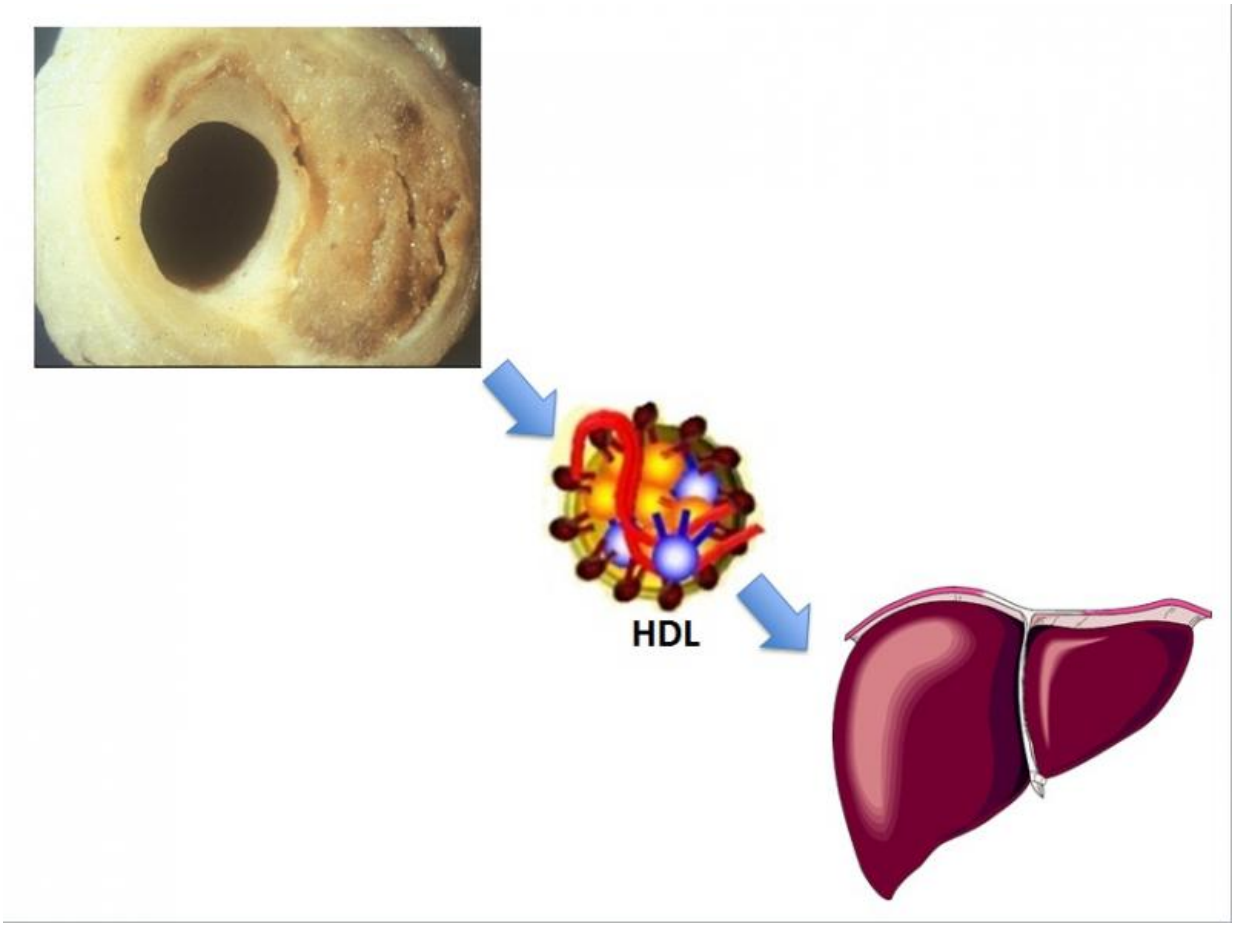
Study shows a form of genetically elevated 'good' cholesterol may actually be bad

March 10 2016



HDL, or 'good' cholesterol, can remove cholesterol from arteries and shuttle it to the liver where it is eliminated, but this process can be disrupted in certain circumstances (such as deficiency of SCARB1). Credit: The lab of Daniel Rader, MD, Perelman School of Medicine, University of Pennsylvania

The generally accepted medical maxim that elevated HDL cholesterol (HDL-C) is "good" has been overturned by a multi-center, international study, led by researchers from the Perelman School of Medicine at the University of Pennsylvania. They show that a certain genetic cause of increased HDL-C may actually be "bad," noting that a specific mutation in a gene which encodes a cell receptor protein that binds to HDL prevents the receptor from functioning. The mutation causes an increased risk of coronary heart disease even in the presence of elevated levels of HDL-C or "good" cholesterol. Their findings are published this week in *Science*.

Previous research raised the possibility that HDL might not be quite as protective against heart disease as generally believed by cardiologists, especially after several clinical trials of HDL-raising drugs showed little or no effect. "The thinking about HDL has evolved recently to the concept that it may not directly protect against all heart disease," said senior author Daniel J. Rader, MD, chair of the department of Genetics. "Our results indicate that some causes of raised HDL actually increase risk for heart disease. This is the first demonstration of a genetic mutation that raises HDL but increases risk of heart disease."

Rader and his colleagues sequenced the lipid-modifying regions of the genomes of 328 people with markedly elevated HDL (along with a control group with lower HDL) to identify genetic causes of high HDL. One of the genes they focused on was SCARB1, which encodes for Scavenger Receptor B1 (SR-B1), the major receptor for HDL on cell surfaces.

In the course of this sequencing, they identified, for the first time, a person without any SCARB1 function, typified by an extremely high HDL-C level of about 150 mg/dL, whereas the normal level is about 50 mg/dL. The subject had two copies of a SCARB1 mutation called P376L, which the team showed caused a breakdown in HDL receptor

function.

Among the many approaches they took, the researchers generated induced pluripotent stem cells (iPSCs) from the SCARB1-deficient person, used them to create liver cells, and showed these new cells had profound reduction in their ability to take up HDL. "This mutation prevents the receptor from getting to the cell surface where it needs to be situated in order to bind and take up HDL," Rader explained. "This disruption in the receptor's job is due to mistakes in its folding and processing during protein synthesis."

Going back to the other sequenced genomes, the researchers were then able to show that persons who carry only one copy of the SCARB1 P376L mutation have significantly higher HDL-C levels. From this, Rader and colleagues had a hunch, based on their knowledge of SCARB1 function and previous studies in mice, that having the SCARB1 P376L mutation, despite raising HDL, might paradoxically increase the risk of heart disease.

Working with other researchers around the world, the Penn team was able to show exactly what they had surmised. "This SCARB1 variant, while rare, is just frequent enough that it allowed us to ask the question about its effect on HDL and heart disease in people with only one copy of the mutation," Rader said.

The Penn team and their colleagues plan to characterize and test other SCARB1 mutations for their relationship to HDL levels and heart disease. Other genes may also have similar effects. "Eventually we may want to perform genetic testing in persons with high HDL to make sure they don't have mutations—like this one—that raise HDL but don't protect against, or may even increase, risk for heart disease," Rader said. Since the P376L mutation in SCARB1 appears to be specific to people of Ashkenazi Jewish descent, testing in this ethnic group might be

particularly important.

Rader suggests that a therapeutic approach to increase the expression or activity of SCARB1 could be a new way to reduce the risk of heart disease even though it would reduce HDL blood levels. "The work demonstrates that the protective effects of HDL are more dependent upon how it functions than merely how much of it is present," Rader concluded. "We still have a lot to learn about the relationship between HDL function and heart disease risk."

More information: "Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease," *Science*, DOI: 10.1126/science.aad3517

Provided by University of Pennsylvania School of Medicine