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An important genetic cardiovascular risk factor explained

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New findings reported in the September issue of *Cell Metabolism*, a Cell Press publication, appear to explain why people who carry specific and common versions of a single gene are more likely to have high cholesterol and to suffer a heart attack. Studies in mice show that the gene, known as sortilin (SORT1), controls the release of LDL (a.k.a. "bad") cholesterol from the liver into the bloodstream.

The findings suggest that SORT1 may be a good target for new cholesterol-lowering drugs, according to the researchers.

"The vast majority - some 95 percent -- of cardiovascular disease is the result of environmental factors modified by genes," said Anders Nykjaer of Aarhus University in Denmark. "Some people can eat a diet enriched in fat, be overweight, and not develop cardiovascular disease. Others can't." SORT1 appears to be one of those important genetic variables, and now the researchers have a pretty good idea why that might be.

The researchers had earlier studied SORT1 in a completely different context. The gene also plays a role in the nervous system. So they were intrigued by the results of genome-wide association studies, which look for associations between common variation in the human genome and diseases or traits, showing that a particular stretch of sequence on chromosome 1 was linked to cardiovascular risk. That sequence covered three genes, including SORT1. (It was not immediately clear which of those three genes was responsible for the rise in cardiovascular risk.)

To investigate SORT1's role further, the researchers created a mouse that lacked SORT1 altogether. That mouse showed 20 percent lower blood cholesterol levels when fed a high-fat Western diet than did normal mice. Importantly, this reduction in cholesterol translated into an approximately 50 to 60 percent reduction in the buildup of plaque in the animals' artery walls. Mice with higher-than-normal levels of SORT1, on the other hand, had higher cholesterol.

If the mice fared better without SORT1 at all, what is it good for? "Everybody says that LDL cholesterol is a bad guy, but you can't do without cholesterol," Nykjaer explains. Cholesterol is a key ingredient in cell membranes and in steroid hormones, for instance. SORT1 facilitates the release of cholesterol into the bloodstream, making that fat available to body tissues that need a certain amount of it.

The problem comes in when you start eating a diet loaded with fat and cholesterol. "Overall, it's good to have sortilin if you don't eat that much," Nykjaer said. "Now, it might be better not to have it all."

Based on the findings, Nykjaer said it might be helpful for people to know what version of SORT1 they carry. Almost a quarter of all people carry the "bad" version of the gene. But he would sooner suggest that everyone live a healthier lifestyle, given that cardiovascular disease is influenced by many factors.

Perhaps the most important implication of the study, he says, is that SORT1 might be a good target for drugs that could block excess cholesterol in the liver, keeping it out of the bloodstream and protecting the heart.

"Lowering LDL cholesterol is considered one of the most efficient strategies to reduce the risk of coronary artery disease," the researchers wrote in conclusion. "Identification of regulators in lipoprotein

metabolism such as sortilin will help to develop therapeutic strategies aimed at reducing plasma LDL cholesterol, the single most predictive cardiovascular risk factor."

Notably, loss of SORT1 doesn't result in a buildup of bad cholesterol in the liver, as one might expect, Nykjaer said. That's because the blocked path to the bloodstream engages other molecular players that dump cholesterol from the liver into bile. In other words, he says, the liver appears to protect itself by ridding the body of that cholesterol.

Provided by Cell Press

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