

# Researchers pinpoint where 'bad' cholesterol levels are controlled

April 17 2009

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Researchers at UT Southwestern Medical Center have found that a protein responsible for regulating "bad" cholesterol in the blood works almost exclusively outside cells, providing clues for the development of therapies to block the protein's disruptive actions.

"The fact that it works mostly extracellularly provides more opportunities to develop different kinds of therapies," said Dr. Jay Horton, professor of internal medicine and [molecular genetics](#) and co-author of the study, which is available online and appears in today's issue of the [Journal of Biological Chemistry](#).

The protein, called PCSK9, disrupts the activity of a key molecule called the low-density lipoprotein receptor, or LDLR. This molecule, which is made and secreted in the liver, latches onto the LDL receptor. This binding, however, triggers a chain of biochemical reactions that leads to the destruction of the LDL receptor. With fewer receptors available, more of the so-called "bad" cholesterol remains in the [bloodstream](#).

Dr. Horton said these new findings show that PCSK9 principally acts as a secreted protein to cause the degradation of LDL receptors.

"Therefore, approaches to block the protein's activity in the blood should be successful in reducing plasma cholesterol levels," he said.

Too much LDL cholesterol in the blood is a major risk factor for heart disease, [heart attack](#) and stroke because it contributes to the buildup of plaque that clogs the walls of [arteries](#). Up to 30 million people

worldwide take a class of drugs called statins to lower their cholesterol to within recommended healthy limits.

To determine whether PCSK9 works inside or outside the cell, the researchers designed peptides - the building blocks of proteins - to jam the interaction between PCSK9 and the LDL receptor. They then added the peptides to a cultured cell medium to see if they could block the activities of PCSK9. The peptides prevented the secreted PCSK9 from binding to the surface of the LDL receptors.

Dr. Horton said the fact that PCSK9 performs its destructive duties outside cells provides more opportunities for drug development.

"It's much easier to design inhibitors of PCSK9 function to work outside a cell than to develop a small molecule that works inside a cell," he said.

The researchers also discovered how a mutation in the LDL receptor causes a condition called hypercholesterolemia in some people. The mutation increases the binding of the LDL receptor to PCSK9, leading to excessive degradation of the receptor and extremely high cholesterol levels. Dr. Horton said degradation is bad news for LDL receptors.

"You want as many of these receptors as possible to clear the LDL from your blood," he said.

Dr. Horton's previous studies have shown that mice lacking PCSK9 have LDL cholesterol levels less than half those of normal mice.

Studies by other UT Southwestern researchers have found that people with mutations in the PCSK9 gene, which prevented them from making normal levels of the PCSK9 protein, had LDL [cholesterol](#) levels 28 percent lower than individuals without the mutation and were protected from developing coronary [heart disease](#). That research was led by Dr.

Jonathan Cohen, professor of internal medicine, and Dr. Helen Hobbs, director of the Eugene McDermott Center for Human Growth and Development.

Dr. Horton said it's now up to pharmaceutical companies to develop drugs that will block these PCSK9 activities. "Our work paves the way for a more active pursuit of antibody and peptide approaches to block the destructive actions of PCSK9," he said.

Other UT Southwestern researchers involved in the current study were senior author Dr. Thomas Lagace, former postdoctoral researcher in molecular genetics; lead author Markey McNutt, graduate student; Dr. Hyock Joo Kwon, assistant professor of biochemistry; Dr. Chiyuan Chen, postdoctoral researcher in molecular genetics; and Justin Chen, summer student research fellow.

The work was supported by the Perot Foundation, the National Institutes of Health, the UT Southwestern Medical Scientist Training Program and the Canadian Institutes of Health Research.

Source: UT Southwestern Medical Center ([news](#) : [web](#))

Citation: Researchers pinpoint where 'bad' cholesterol levels are controlled (2009, April 17) retrieved 23 April 2024 from <https://phys.org/news/2009-04-bad-cholesterol.html>

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