

U-M researchers find new way to clear cholesterol from the blood

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Researchers at the University of Michigan have identified a new potential therapeutic target for lowering cholesterol that could be an alternative or complementary therapy to statins.

Scientists in the lab of David Ginsburg at the Life Sciences Institute inhibited the action of a gene responsible for transporting a protein that interferes with the ability of the liver to remove cholesterol from the blood in mice. Trapping the destructive protein where it couldn't harm receptors responsible for removing cholesterol preserved the liver cells' capacity to clear plasma cholesterol from the blood, but did not appear to otherwise affect the health of the mice.

In the research, published April 9 in the online journal *eLife*, scientists found that mice with an inactive SEC24A gene could develop normally. However, their plasma cholesterol levels were reduced by 45 percent because vesicles from liver cells were not able to recruit and transport a critical regulator of [blood cholesterol levels](#) called proprotein convertase subtilisin/kexin type 9. PCSK9 is a secretory protein that destroys the liver cells' receptors of [low-density lipoprotein](#)— LDL, the so-called "[bad cholesterol](#)"—and prevents the cells from removing the LDL.

"Inhibiting SEC24A or PCSK9 may be an alternative to statins, and could work together with statins to produce even greater effects," said Xiao-Wei Chen of the Ginsburg lab, the first author on the paper. "Also, they might be effective on patients who are resistant to or intolerant of statins."

Initial studies of anti-PCSK9 therapies in humans have shown that eliminating PCSK9 can lower cholesterol dramatically and work with statins like [Lipitor](#) to lower it even further. The Ginsburg lab's research points to a new area for study: rather than inhibiting PCSK9 itself, perhaps future therapies could block the transport mechanism that allows the destructive protein to reach the LDL receptors.

The paper, "SEC24A deficiency lowers [plasma cholesterol](#) through reduced PCSK9 secretion," explains the mechanism by which cells transport PCSK9. Vesicles transport proteins in the cell; the Ginsburg lab's research focused on a specialized type of vesicle packaged by the Coat Protein Complex II, which regulates the metabolism of cholesterol, among many other things. These [vesicles](#) selectively transport cargo proteins including PCSK9.

Without those LDL receptors (LDLR), [liver cells](#) are not able to remove LDLs from the bloodstream, so protecting the LDLR from PCSK9 would allow the receptors to continue to remove cholesterol.

"Without SEC24A, much of the PCSK9 couldn't make its way out of the cells to destroy the LDLR, which then clears cholesterol from the blood," Chen said.

The part of the vesicle that selects which proteins to transport is SEC24. By blocking SEC24A gene, the researchers disabled the vesicle's selection of PCSK9. The destructive protein remained trapped within the cells, leaving the LDLR intact and enabling the liver to clear the body of cholesterol that otherwise could accumulate in arteries.

"We have no reason at this point to expect that this strategy will be any better than anti-PCSK9 therapy for treating high [cholesterol](#), but it would be another alternative approach, and it's hard to predict which drugs will work the best and be the safest until we actually try them out

in people," Ginsburg said.

Ginsburg is a research professor at the Life Sciences Institute, where his laboratory is located. He is also the James V. Neel Distinguished University Professor and the Warner-Lambert/Parke-Davis Professor in the Division of Molecular Medicine and Genetics, Department of Internal Medicine and departments of Human Genetics and Pediatrics at the U-M Medical School and a Howard Hughes Medical Institute Investigator.

More information: elifesciences.org/content/2/e00444

Provided by University of Michigan

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