SOUTHWESTERN NEWS

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## Study reveals potential new target for cholesterol-lowering drugs

DALLAS – March 29, 2005 – Mice lacking a key protein involved in cholesterol regulation have low-density lipoprotein, or "bad" cholesterol, levels more than 50 percent lower than normal mice, and researchers suggest that inhibiting the same protein in humans could lead to new cholesterol-lowering drugs.

In a study to be published in the *Proceedings of the National Academy of Sciences* and available online this week, researchers at UT Southwestern Medical Center deleted the *Pcsk9* gene in mice. The gene, present in both mice and humans, makes the PCSK9 protein, which normally gets rid of receptors that latch onto LDL cholesterol in the liver. Without this degrading protein, the mice had more LDL receptors and were thus able to take up more LDL cholesterol from their blood.

"The expression of LDL receptors is the primary mechanism by which humans lower LDL cholesterol in the blood," said Dr. Jay Horton, associate professor of internal medicine and molecular genetics and senior author of the study. "This research shows that in mice, deleting the PCSK9 protein results in an increase in LDL receptors and a significant lowering of LDL cholesterol."

High LDL cholesterol 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. Nearly 25 million people worldwide take a class of drugs called statins to lower their cholesterol to within recommended healthy levels.

On average, mice lacking the *Pcsk9* gene, called knockout mice, had blood LDL cholesterol levels of 46 milligrams per deciliter, while wild-type mice had levels around 96 mg/dl, a difference of 52 percent.

Dr. Horton's research is consistent with findings from another recent UT Southwestern study showing that humans with mutations in their *PCSK9* gene, which prevented them from making normal levels of PCSK9 protein, had LDL cholesterol levels 40 percent lower than individuals without the mutation. That study, based on data gathered from nearly 6,000 participants in the Dallas Heart Study, was published in February in *Nature Genetics*. The research was led by Dr. Helen Hobbs, director of the Dallas Heart Study and of the Eugene McDermott Center for Growth and Development, and Dr. Jonathan Cohen, associate professor of internal medicine.

"The lower cholesterol levels of humans with mutations in *PCSK9*, combined with the results of our studies in mice, suggest that variations in the levels of the PCSK9 protein significantly affect blood

cholesterol levels, and compounds that inhibit this protein may be useful for the treatment of high cholesterol," Dr. Horton said.

Dr. Horton and his colleagues also gave their knockout mice statins, which further enhanced the clearance of LDL cholesterol from their blood. The findings suggest new drugs targeting PCSK9 may be able to act in conjunction with statin drugs to further lower LDL cholesterol levels. Dr. Horton said cholesterol-lowering drugs based on blocking PCSK9 might be effective on their own as well, providing another option for individuals unable to take statins.

Statins increase the activity of a protein called SREBP-2, which activates the creation of more LDL receptors; however, Dr. Horton's previous studies found that SREBP-2 also boosts the activity of the PCSK9 protein, which degrades those receptors.

"We looked at these competing effects and thought that if we removed the PCSK9 component completely, we would get a further increase in LDL receptors, and that's what happened," he said.

The competing systems may have evolved to keep the body's cholesterol levels fine-tuned and to minimize big swings in cholesterol content in normal cells, Dr. Horton said. Too much or too little cholesterol can damage or kill cells. He and his colleagues next will try to determine just how the PCSK9 protein degrades the LDL receptors.

Dr. Horton said the current study's results also are important because many researchers thought there might be no new ways to exploit the LDL receptor pathway as a means of lowering LDL cholesterol.

"Our research, and that of Dr. Hobbs and her colleagues, further emphasize the importance of the LDL receptor in cholesterol regulation," Dr. Horton said.

UT Southwestern researchers Dr. Michael Brown, director of the Erik Jonsson Center for Research in Molecular Genetics and Human Disease, and Dr. Joseph Goldstein, chairman of molecular genetics, shared the 1985 Nobel Prize in physiology or medicine for their discovery of the LDL receptor.

Other UT Southwestern researchers who participated in the *PNAS* study were Dr. Shirya Rashid, molecular genetics postdoctoral research fellow; Dr. David Curtis, surgery postdoctoral researcher; Dr. Rita Garuti, visiting senior fellow; Norma Anderson, molecular genetics senior research associate; Drs. Yuriy Bashmakov, Young-Ah Moon and Yiu Kee Ho, assistant professors of molecular genetics; and Dr. Robert E. Hammer, professor of biochemistry.

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