SOUTHWESTERN NEWS

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**UT SOUTHWESTERN RESEARCHERS DISCOVER NEW MECHANISM BY WHICH HDL PROTECTS ARTERIES**

DALLAS – July 2, 2001 – Scientists at UT Southwestern Medical Center have discovered that high-density lipoprotein (HDL) – the "good cholesterol" – triggers a process that keeps arteries clean and flexible.

It's a discovery, researchers believe, that could lead to new strategies to prevent or treat vascular diseases such as atherosclerosis, commonly known as hardening of the arteries.

"What we have found is that HDL is a robust stimulator of nitric oxide production in endothelial cells, which are the thin layer of cells lining the arterial wall," said Dr. Philip W. Shaul, professor of pediatrics, senior author of the study and holder of the Lowe Foundation Professorship in Pediatric Critical Care Research.

Nitric oxide, he said, is a potent signaling molecule that keeps arteries clean and flexible, thereby preventing them from clogging and constricting, processes that restrict blood flow and lead to high blood pressure, strokes and heart attacks.

The study, reported in the July issue of *Nature Medicine*, describes the mechanism by which HDL stimulates the enzyme responsible for nitric oxide production. Researchers used cells and arteries from sheep and genetically engineered mice, all of which have characteristics similar to those of humans, Shaul said.

He cited these details of the study's major findings:

-- One of the major protein components of HDL, apolipoprotein A-I, which is protective against atherosclerosis in humans, is crucial to stimulating nitric-oxide production.

-- Another protein, known as scavenger receptor-BI, which enables the HDL particle to bind to the cell surface, is absolutely required for nitric-oxide production.

-- The entire process is localized to microscopic pockets known as caveolae, located in the outer membranes of the endothelial cells that line the arterial wall.

"Our previous understanding has been that HDL serves as a taxi, a shuttle system for

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cholesterol," Shaul said, "delivering it from peripheral tissues, including blood vessels, to the liver and other organs where it is starting material for steroid hormones or where it is excreted."

The current study, he said, reveals an entirely new mechanism by which HDL provides even more benefits to vascular health.

"HDL is the most potent stimulator of nitric-oxide production that we have found in the past decade," Shaul said. "What we're realizing is that, not only is it a taxi, but that it hits the arterial walls, and it causes a dramatic response by the arterial walls to produce nitric oxide."

He cited a previous study, reported last year, that showed that under abnormal conditions, the HDL "taxi" can reverse its route to deliver cholesterol to diseased endothelial cells. As a result, the cells remain capable of producing nitric oxide.

"HDL is an incredibly intricate guardian of the arterial wall, and we still have much to learn about it," Shaul said.

Ivan Yuhanna, research associate in pediatrics at UT Southwestern, was lead author of the report. Other UT Southwestern researchers included Dr. Richard G.W. Anderson, chairman of cell biology; Dr. Helen H. Hobbs, director of the Eugene McDermott Center for Human Growth and Development and chief of medical genetics; Dr. Blair E. Cox, assistant professor of pediatrics; Lisa D. Hahner, senior research associate in pediatrics; and Sherri Osborne-Lawrence, research scientist in pediatrics.

The research team also included Dr. Yan Zhu and Dr. Michael E. Mendelsohn of the Tufts University School of Medicine and Dr. Yves L. Marcel of the University of Ottawa Faculty of Medicine.

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