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****UTHSCD researchers identify another basic cause of high cholesterol

DALLAS -- The roots of coronary heart disease often lie in the inability to clear excess cholesterol from the bloodstream. It can form fatty deposits that clog arteries. Why one person's body clears cholesterol efficiently and another doesn't is a major challenge to medical scientists.

Researchers at The University of Texas Health Science Center at Dallas have been leaders in explaining cholesterol metabolism. Now Drs. Gloria Lena Vega and Scott Grundy have discovered how a defect in the molecular structure of LDL, the "bad" cholesterol, can contribute to heart disease.

Cholesterol is cleared from the blood by being taken into individual cells, especially liver cells. This happens when a cholesterol-carrying particle called a low density lipoprotein (LDL) attaches to a receptor molecule on the cell's surface and is drawn into the cell.

"The process works like a lock and key," said Vega. "Each particle of LDL has a specialized protein on its surface called apo-B that recognizes the receptor. The apo-B is the only key that fits into the lock--the LDL receptor--that admits LDL into a cell."

Drs. Joseph Goldstein and Michael Brown of UTHSCD won a Nobel Prize in 1985 for the describing the process, which is called receptor-mediated endocytosis. They were investigating a gene-linked condition in which people build up high levels of blood cholesterol. They discovered that the condition, called familial hypercholesterolemia (FH), results from insufficient LDL receptors. FH affects about 1 in 500 people.

"In people with FH, the lock is broken. They account for about 10 percent of the people who have heart attacks before the age of 60," explained Grundy. "Our challenge now is to account for the other 90 percent. This new research shows that some people have a defective key, that is, an abnormal apo-B."

Grundy, professor of internal medicine and biochemistry at UTHSCD, and Vega, a biochemistry instructor, tested 20 patients at the Dallas Veterans Administration Medical Center to discover if poor clearance of cholesterol from the blood could result from defective apo-B as well as from inadequate receptors.

Fifteen of the patients had moderate hypercholesterolemia, with total cholesterol levels between 250 and 300 milligrams per deciliter. Although 11 had coronary heart disease, none had recently had heart attacks or were being treated with drugs to lower cholesterol. None had high triglyceride levels or classical symptoms of FH.

The other five patients had been diagnosed as having FH. They had higher cholesterol levels, early onset of coronary heart disease, tendon xanthomas (fatty, wart-like deposits on tendons) and at least one near relative with equally high LDL cholesterol.

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The researchers took blood samples from each of the volunteers. They also took blood samples from healthy medical students with desirable levels of LDL. The LDL was isolated from the blood samples and tagged with a marker. Then each subject was re-injected with his own LDL as well as some from one of the donors. Subsequent blood samples were taken over the next 14 days to determine the rate at which LDL cholesterol was cleared from the blood. Details of the tests were published in the November 1986 Journal of Clinical Investigation.

As expected, the FH patients cleared both their own and donor LDL at very slow rates because their problem was a lack of receptors. Their LDL particles were presumably normal. Ten of the other 15 non-FH patients also showed no appreciable difference in the length of time it took for both the donor and their own LDL to be cleared from the blood.

However, the final five non-FH patients showed a marked difference between their own and donor LDL. Donated LDL was cleared from the blood at a rate equaling that of people with normal LDL levels. On the other hand, their own LDL was cleared at a significantly lower rate, showing that the LDL was not binding to receptors as it should.

Vega and Grundy suggested two causes for the abnormal binding. Most likely, the structure of the apo-B is defective, causing it to attach poorly to receptors. Several laboratories are looking at the amino acid sequence in apo-B at this time to see if the apo-B from different individuals might vary. A less likely cause of abnormal LDL binding might lie with defects in other components of the LDL, such as the protein apo-E, lipids or carbohydrates.

"Our study proves that a defect in LDL results in hypercholesterolemia for some people although it is not the cause for most people with high cholesterol levels. There are many ways LDL metabolism can go wrong, and this is one of them. Being able to identify the people with defective LDL might prove beneficial in determining their treatment. In addition, the method we used for this research should be helpful in further studies involving the structure of apo-B," concluded Grundy.

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Note: The University of Texas Health Science Center at Dallas comprises Southwestern Medical School, Southwestern Graduate School of Biomedical Sciences and the School of Allied Health Sciences.