# SOUTHWESTERN NEWS

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## NEW RECEPTOR FOUND THAT SPEEDS CHOLESTEROL METABOLISM

DALLAS – October 31, 1996 – A team of scientists at UT Southwestern Medical Center at Dallas have discovered a protein that speeds cholesterol metabolism in response to the amount of cholesterol the protein senses.

The finding could help scientists develop new drugs for controlling cholesterol and perhaps even for new male and female contraceptives.

The protein -- a nuclear receptor named LXR-alpha -- is signaled by biochemicals called oxysterols, which are produced when cholesterol levels in the body are high, reported Dr. David Mangelsdorf in the Oct. 24 issue of the journal *Nature*. Scientists believe the receptor activates and regulates enzymes that break down cholesterol for conversion to bile acids and steroid hormones.

"What we have discovered is a potentially different way for regulating cholesterol, and that's by speeding up the reactions that affect its metabolism," said Mangelsdorf, assistant professor of pharmacology and assistant investigator in the Howard Hughes Medical Institute (HHMI) at UT Southwestern.

The research is significant because it has not been known how the body speeds up cholesterol metabolism to avoid premature atherosclerosis, or cholesterol buildup in the arteries, which leads to heart attacks. However, another pathway that regulates cholesterol levels in the bloodstream is well-documented: When cholesterol levels are high in a normal person, a feedback mechanism represses cholesterol and LDL receptor synthesis.

Mangelsdorf's work shows that instead of preventing the synthesis, this new pathway increases the rate at which cholesterol is degraded. One enzyme that may be involved in changing cholesterol to other cellular functions is called 7-alpha hydroxylase, which converts cholesterol to bile acids.

LXR-alpha is a member of the family of nuclear hormone receptors. LXR stands for

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"liver orphan receptor" because it is found most often in the liver although it is also expressed in the pituitary glands, fat, kidneys, intestines and adrenal glands. It is called an orphan receptor because scientists did not know what ligand or hormone it interacted with to create cellular changes.

Discovery of LXR-alpha, if it is indeed a true receptor, is only the third such orphan receptor for which a hormonal ligand has been found. Scientists believe there are 30 to 60 orphan receptors whose functions are unknown.

"The question now is, 'What do these orphan receptors do, especially if they have a novel hormonal ligand?' It suggests that an entirely new endocrine system might exist for hydroxycholesterols, the signaling molecules," Mangelsdorf said. "We also want to know if they bind directly to LXR-alpha."

He said that because oxysterols also are produced in the ovaries and the testes, LXR-alpha or a similar receptor may regulate the maturation of egg and sperm cells. The process begins when a mechanism tells the cells around the eggs to secrete a hormonal substance called FF-MAS, which is one of the oxysterols identified to activate LXR-alpha.

"The implication is that if LXR-alpha is actually mediating oocyte maturation, it's the perfect target for a contraceptive drug," said Mangelsdorf. He cautioned, however, that this is still highly hypothetical.

The other researchers involved in this work included UT Southwestern scientists Dr. J. Russell Falck, associate professor of molecular genetics and holder of the Eugene McDermott Distinguished Chair in Molecular Genetics; Dr. Thota Rama Devi, molecular genetics research fellow and HHMI research associate; and graduate students Bethany Janowaski and Patricia J. Willy.

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