SOUTHWESTERN NEWS

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UT SOUTHWESTERN NOBELISTS UNCOVER PROTEIN STRUCTURE THAT MAY LEAD TO ADVANCES AGAINST HIGH CHOLESTEROL

DALLAS – Dec. 6, 2002 – Three of UT Southwestern Medical Center's Nobel laureates and their colleagues have solved a protein structure that someday could lead to advances against diseases caused by high cholesterol.

Nobelist Dr. Johann Deisenhofer, professor of biochemistry and senior author of the study, and Dr. Gabrielle Rudenko, assistant instructor of biochemistry and lead author of the study, solved the three-dimensional structure of a low-density lipoprotein (LDL) receptor's extracellular domain. LDL is known as the "bad" cholesterol because it deposits fat-like substances that clog arteries.

The LDL receptor binds LDL in the liver and clears it from the blood by pulling cholesterol inside the cells, where it is metabolized to replenish hormones, the cell membrane, vitamin D and other products.

"This research will help scientists understand the mechanics of how our bodies absorb cholesterol from the blood," Deisenhofer said. "Hopefully, we can use the information to develop treatments for people with mutations that diminish the functions of their LDL receptors."

UT Southwestern Nobel laureates Dr. Michael Brown and Dr. Joseph L. Goldstein also assisted in the study, which will be published in the Dec. 20 issue of *Science.* An early version is listed online at *Science Express.*

There are about 1,000 LDL receptor mutations that have been found in people with familial hypercholesterolemia (FH). FH is one of the most common "single-gene" inherited diseases and affects about one in every 500 people, Rudenko said. By revealing the structure of the receptor, scientists now can begin to understand why these different mutations cause FH, a disorder that results in very high cholesterol levels, atherosclerosis and increased risk of having a heart attack early in life.

"If you understand the basic biological mechanisms underlying a disease, you can hope

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to come up with strategies to battle that disease," Rudenko said. "Solving three-dimensional structures of proteins causing or involved in a particular disease can help scientists understand how these protein actually work and the role they play in the particular disease. In some cases protein structures can even be used to design drugs."

Earlier research by Brown and Goldstein, who shared the 1985 Nobel Prize in physiology or medicine for discoveries concerning the regulation of cholesterol metabolism, found that at a neutral pH on the cell surface, the LDL receptors bind LDL. After the receptors laden with LDL are internalized in the cell – in a process known as receptor-mediated endocytosis – the receptor releases its LDL in cellular compartments that are acidic and then returns to the plasma membrane, where it is "recycled."

The LDL receptor's extracellular domain consists of two major parts, the LDL binding region and the so-called "beta-propeller" region. In the *Science* study, the structure reveals that parts of the LDL binding region attach to the "beta-propeller" region at low pH and thus cannot bind to LDL. It looks as if the "beta-propeller" region competes with LDL, Deisenhofer said.

"The LDL receptor is crucial to clearance of LDL and in keeping your cholesterol levels healthy," Rudenko said.

Deisenhofer received the 1988 Nobel Prize in chemistry for research using X-ray crystallography to reveal in three-dimensional detail the structure of protein in the membrane of cells. His continuing work on understanding the detailed structure of important biological molecules makes possible the development of a new generation of drugs and vaccines. He holds the Virginia and Edward Linthicum Distinguished Chair in Biomolecular Science and is an investigator in the Howard Hughes Medical Institute.

The work was supported by the Perot Foundation and the National Institutes of Health.

Other researchers on the *Science* study were from Lawrence Berkeley National Laboratory and New York University School of Medicine.

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