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New Drugs Could Be More Effective at Lowering Cholesterol

Researchers have discovered two targets for a new generation of cholesterol-lowering drugs that should allow greater precision in managing cholesterol levels.

Howard Hughes Medical Institute (HHMI) investigator David J. Mangelsdorf and colleague Joyce J. Repa, an HHMI associate at the University of Texas Southwestern Medical Center, have switched off cholesterol uptake in mice using a drug that targets key cholesterol-governing receptors. Their experiments also reveal how the receptors, LXR and FXR, control genes that regulate the body's cholesterol balance. Scientists from Tularik Inc., in South San Francisco and Ligand Pharmaceuticals in San Diego also collaborated on the research, which was published in the September 1, 2000, issue of the journal *Science*.

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"Before this work, there were only hints that a protein-mediated mechanism for cholesterol uptake existed," said Mangelsdorf. "We believed that the process was not just a passive absorption through the cell membrane, but we needed proof to support this idea. Although the results from these studies in mice are promising, there's a long road ahead before these compounds can be considered for human clinical trials."

A key clue that cholesterol uptake is actively regulated emerged from studies showing that mice can selectively avoid absorbing ingested plant sterols, which have a chemical structure that is similar to cholesterol. A second clue came from the observation that strains of rats and mice differ in their ability to absorb cholesterol, suggesting that there is a genetic component to control of cholesterol metabolism.

Mangelsdorf said his team's current work began not as a search for the mechanism of cholesterol uptake, but as an effort to identify the hormone-like compounds—called ligands—that activate LXR and FXR. These two orphan nuclear receptors are proteins that have the ability to turn on genes in the nucleus, but their triggers remained unknown, hence the term "orphan."

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In previous work, the scientists had shown that LXR and FXR were involved in disposing of excess cholesterol and in regulating bile acids. When the group knocked out the LXR genes in mice, they found that LXR controlled a key enzyme that produced bile acids from cholesterol. Bile acids are generated to shed excess cholesterol and to speed cholesterol absorption by making cholesterol more soluble.

"An important take-home lesson here is that because we could show that these nuclear receptors had very direct and specific actions on cholesterol balance, they are excellent targets for drugs to affect cholesterol levels," said Mangelsdorf. "Like many other such nuclear receptors, they are affected by drugs that can be taken orally and go right to the receptors."

The group's next step was to see whether turning on LXR or FXR could affect cholesterol uptake. While the scientists didn't initially have a drug that turned on either LXR or FXR, they did know that the compound LG268 activates RXR, a protein that is required for both LXR and FXR activity. RXR latches on to both LXR and FXR, and helps them activate their target genes.

"Drugs like LG268 are especially promising because they are already being considered for clinical use for chemotherapy and diabetes," said Mangelsdorf. "But there had been no reason to test the drug's effect on cholesterol metabolism because nobody knew about LXR and FXR. The development of drugs that specifically activate LXR or FXR may prove even more beneficial."

When Mangelsdorf and his colleagues treated mice with LG268, they found that the drug completely blocked the animals' absorption of cholesterol. "This was an astounding and dramatic effect," said Mangelsdorf. "And it prompted us to try to understand both how the drug inhibited cholesterol absorption in the intestine and promoted excretion of excess cholesterol."

In extensive biochemical and genetic experiments on mice, the scientists showed that LG268 enhances FXR's ability to repress a gene crucial for bile acid synthesis, thus reducing cholesterol absorption by interfering with its solubility. They also found that LG268 activated LXR's ability to speed up production of ABC1, a reverse cholesterol transporter that moves excess cholesterol out of cells to the liver for excretion.

"We have discovered a potential therapeutic mechanism for regulating cholesterol absorption from the diet and resorption of circulating cholesterol. Also, we have identified a mechanism of cholesterol transport in the intestine and the potential regulated transporter," said Mangelsdorf.

Although LG268 does induce fatty acid synthesis—an unwanted side effect—Mangelsdorf believes that it may provide an excellent foundation for the rational design of LG268-like compounds that do not have side effects. This new generation of drugs to prevent cholesterol absorption could work in concert with current cholesterol-lowering drugs that inhibit internal cholesterol synthesis by the body. Such cholesterol-synthesis-inhibiting drugs, called statins, achieve a significant cholesterol-lowering effect, but they do not work for everyone since the body continues to absorb cholesterol from the diet.

"Using both kinds of drugs could actually produce a net loss of cholesterol in the body," said Mangelsdorf. "By carefully monitoring drug dosages and cholesterol levels, you could essentially 'dial-in' exactly the level you wanted a person's cholesterol level to be."

In future work, the scientists will aim to improve their understanding of the LXR- and FXR-regulatory machinery. They will also concentrate on figuring out how ABC1 works. In transporting cholesterol out of cells, ABC1 also eliminates cholesterol from immune cells called macrophages. These cells are the culprits that form artery-clogging fatty atherosclerotic plaques that can trigger heart attacks. Thus, using drugs to activate ABC1 may prevent plaque buildup, said Mangelsdorf.