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NEWS

THE UNIVERSITY OF TEXAS
(SOUTHWESTERN)
MEDICAL SCHOOL AT DALLAS

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DALLAS--Scientists here have tracked a basic defect which causes a cancer cell's cholesterol-regulating "thermostat" to go awry.

A normal body cell has a regulating mechanism which keeps it from producing too much or too little cholesterol. But a cancer cell apparently loses this "feedback" control at a time and site pinpointed for the first time by a research team headed by Dr. Marvin D. Siperstein at The University of Texas (Southwestern) Medical School.

An enzyme called mevalonate synthetase is involved in the loss of feedback control in production of cholesterol by cancerous liver cells in rats, according to the researchers' article in the lastest Proceedings of the National Academy of Science.

This breakdown is "the only known consistent defect in the control mechanism of cancer," said Dr. Siperstein, professor of internal medicine at Southwestern.

Dr. Siperstein termed the discovery "an important step" which tells researchers where--but not how or why--the chemical breakdown occurs.

"Now," he said, "we know exactly where the problem lies. We have to see what's wrong with that enzyme by isolating it, analyzing it; and we hope thereby to see whether loss of the key controlling mechanisms (cholesterol feedback) can be ascribed to a specific defect in a specific protein."

Thus an investigation that began five years ago as an almost accidental offshoot of heart research becomes an intensified probe into the mysteries of cancer cells' chemical malfunctions--with hoped-for implications aiding both basic knowledge and treatment of the disease.

"This study may have fundamental importance in determining what biochemical changes underly cancer, and it may offer a means of testing for cancer--but both of these are in the future," Dr. Siperstein said.

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The UTSMS scientists already can diagnose liver cancer in laboratory animals with their cholesterol-measuring technique, and a "simple blood test" similar to current thyroid examinations could one day evolve to diagnose liver cancer (and, possibly, other forms) in humans, he believes.

Liver cancer was chosen for the experiments, Dr. Siperstein explained, because "it is a good one to study."

"We know so much about the biochemistry of the liver. The slow-growing tumors offer a model for studying other cancers, and what is true of liver cancer probably will be true of other cancers," he said. (Liver cancer, rare in the United States, is one of the commonest forms of human cancer worldwide.)

Studies so far have concentrated on liver cancer in animals, but similar preliminary results have been obtained also in animals with leukemia, the scientist said. Experiments are being extended presently to breast cancer.

Only tests involving humans so far have been biopsies (microscopic examinations) of a few liver tumors, Dr. Siperstein said. The resulting data, while inadequate for sound scientific conclusions--is nonetheless encouraging.

"We found that this feedback system had been destroyed in human beings," Dr. Siperstein said.

Dr. Siperstein compared the feedback system with a thermostat:

"You feed cholesterol, cholesterol synthesis stops. This represents what is termed 'feedback control' or thermostatic control of cholesterol synthesis, and the process serves to keep the level of cholesterol on the body normal as a thermostat keeps the temperature in a room normal."

The most recent studies identified the particular enzyme or change-causing chemical involved in this thermostatic process.

"We had a lot of indirect evidence that this probably was the enzymatic site," he explained. "We took normal and cancer tissue from livers of rats and, using tracer materials, specifically measured the critical enzyme mevalonate synthetase.

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"And we showed that in a normal animal liver upon being fed cholesterol, this enzyme decreased enormously"--indicating the chemical "thermostat" was working.

"But in cancer tissue, the enzyme level didn't change at all. That means that it was this enzyme that is responsible for the synthesis, and that it has become insensitive to thermostatic control."

The result is continued production by the enzyme of a chemical called mevalonate, which is manufactured in the cancerous tissues.

The Dallas researchers stumbled onto the intriguing cholesterol-cancer link while studying the fatty substance's better known relationship, that with blood vessel and heart disease.

Armed with a grant from the National Institutes of Health to study athersclerosis, Dr. Siperstein and his associates began studying the control of cholesterol synthesis, in an effort to find out why cholesterol levels are high in many heart patients.

In the process, they discovered the key enzyme suspected of controling the feedback regulation.

"And then, almost by chance, we decided to look and see whether cancer tissue could synthesize cholesterol," he related. "Much to our surprise, cancer not only produced cholesterol, but made too much of it."

Dr. Siperstein queried the NIH, and the federal agency readily agreed that the work should switch into this promising new direction. So the original heart-disease study was virtually abandoned to other researchers.

"This work illustrates the fundamental wisdom of the National Institutes of Health's policy of allowing investigators to follow interesting leads, even though those leads may have nothing to do with the original research project," he observed.

"A more restrictive policy, forcing scientists to do only what they agreed to do, would have prevented us from ever making this study."

Experiments with rainbow trout, widespread victims of liver cancer blamed on the chemical aflatoxin, confirmed that the cholesterol mechanism was knocked out by the chemical long before any trace of cancer appeared--indicating, Dr. Siperstein said, that the defect precedes the disease and not the other way around.

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This fact, plus knowledge that the cholesterol malfunction is the only known such defect consistently occuring in cancer, leads the scientists to the obvious--but so far unanswerable--question:

Do the uncontrolled cholesterol output and the cancer process itself--also a process of uncontrolled growth--stem from the same ~~facu~~ Sault ty enzymatic "thermostat"?

In this question is sufficient scientific challenge to fuel laboratory labors at UTSMS for years to come.

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