SOUTHWESTERN NEWS

Media Contact: Wayne Carter
or Susan Morrison
214-648-3404
wayne.carter@utsouthwestern.edu
susan.morrison@utsouthwestern.edu

EMBARGOED UNTIL 1 P.M. CDT THURSDAY, MAY 16, 2002

RESEARCHERS UNCOVER BIOCHEMICAL CONNECTION BETWEEN HIGH-FAT DIETS AND INCREASED COLON-CANCER RISK

DALLAS – May 17, 2002 – Researchers at UT Southwestern Medical Center at Dallas have uncovered what could be a key clue in tracing the connection between high-fat diets and increased colon-cancer risk.

Their findings, published in today's edition of *Science*, reveal that the body's natural mechanisms aren't built to handle lithocholic acid, a toxic byproduct of dietary fat, in the volume generated by high-fat diets.

Dr. David Mangelsdorf, professor of pharmacology and investigator in the Howard Hughes Medical Institute (HHMI) at UT Southwestern, said observational evidence established a strong association between high-fat diets and colorectal cancer, but scientists could not explain the biological and biochemical mechanisms that formed the link.

"The rate of colorectal cancer is much higher in the United States – where a high-fat diet is common – than in Japan, where people don't eat a lot of fat and colorectal cancer is almost nonexistent. But no one has understood why that is," he said.

The new findings show that at least part of the answer lies in the body's inability to cope with large amounts of lithocholic acid, produced when the body processes cholesterol. The body produces bile acids when it breaks down cholesterol, part and parcel of dietary fat. Those bile acids go to the small intestine and are broken down into secondary bile acids, one of which is lithocholic acid.

Most secondary bile acids circulate to the liver, but only a little bit of lithocholic acid does so. Much of it remains in the small intestine, then moves into the colon, or large intestine.

(MORE)

"Lithocholic acid is highly toxic, and it builds up in a high-fat diet," Mangelsdorf said. "We don't know how it causes cancer; but it is known to cause cancer in mice, and people with colon cancer have high concentrations of it."

Scientists knew that a certain receptor controlled the small amount of lithocholic acid in the liver. Receptors are proteins that bind to certain substances to help the body absorb or get rid of them. The lithocholic acid-controlling receptor also is present in the colon. But there isn't enough of it to cope with large volumes of lithocholic acid.

However, the lithocholic acid-controlling receptor is similar in structure to another receptor, which binds to vitamin D to help the body absorb calcium. Mangelsdorf's team wondered if the vitamin D receptor might also help eliminate lithocholic acid.

The researchers discovered that the vitamin D receptor actually plays a major role in eliminating lithocholic acid. Like the receptor that works in the liver, the vitamin D receptor binds to lithocholic acid, then binds to a specific gene, called *CYP3A*. That triggers production of an enzyme that breaks down the toxic acid. Those findings were made using assays, which are small, flat panels used to study genetic activity outside living organisms.

Next, the researchers used tissue cultures to show that the process is replicated in living cells. Then, the team fed vitamin D and lithocholic acid to mouse models. The lithocholic acid activated the animals' *CYP3A* genes, as well as other genes that the vitamin D receptor is known to bind to after binding with vitamin D.

"It turned out that *in vivo*, the vitamin D receptor appeared to play a large role in breaking down lithocholic acid," Mangelsdorf said.

While the research identifies a possible target for helping the body eliminate excess lithocholic acid, exploiting the research might not be so simple. Taking extra vitamin D would stimulate more activity in the vitamin D receptors, but that also would cause the body to absorb more calcium. Ingesting too much vitamin D can lead to hypercalcemia, a toxic condition that occurs with excessive calcium buildup.

Mangelsdorf said the body's natural lithocholic acid-response mechanism simply wasn't

(MORE)

built to handle the amount of fat in the modern American diet.

"Our bodies can handle slight changes in lithocholic acid that come from a normal diet, but not a high-fat diet," he said. "The current American diet can provide more fat on a daily basis than a human being was ever meant to handle."

Dr. Makoto Makishima, a former research associate in the HHMI at UT Southwestern, was lead author of the study. Other UT Southwestern researchers who contributed were Timothy T. Lu, an M.D./Ph.D. student in pharmacology, and Dr. Hideharu Domoto, a postdoctoral fellow in pharmacology. Other institutions contributing to the study were the Salk Institute for Biological Studies and the University of Arizona College of Medicine.

The study was supported by the Howard Hughes Medical Institute, the National Institutes of Health, the Robert A. Welch Foundation and the Human Frontier Science Program.

###