

THE PLAIN DEALER

Northeast Ohio

THURSDAY
JULY 23, 1998

Gene may hold key to fighting colon cancer

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PLAIN DEALER REPORTER

A team of Cleveland researchers has pinpointed a gene that, when it becomes defective and shuts down, causes colon cancer in people with no family history of the disease.

The researchers at University Hospitals' Ireland Cancer Center and Case Western Reserve University also have found that an experimental drug, although toxic to humans, can switch the gene on again and make cancerous cells easier to kill.

It is possible a safer form of the drug could be used to prevent colon cancer, the leader of the research team said.

"We'd like to find a version of this drug that has no side effects that you could give to people who were at risk of getting cancer to prevent it from happening in the first place," said Dr. Sanford

Markowitz, a cancer specialist at University Hospitals and professor of cancer genetics at CWRU.

The research results were published this week in the medical journal "Proceedings of the National Academy of Sciences."

The findings were made after analyzing tissue samples from colon cancer patients at the Ireland Cancer Center. The patients developed symptoms in their 50s or 60s, the age at which the most common form of colon cancer typically occurs.

The study focused on a previously identified gene called hMLH1, which is known to play a role in causing colon cancer in people with a family history of the disease. The study led by Markowitz found that the hMLH1 gene also is involved in cancer development in people with no family history of colon cancer.

"Now we know that when this gene is not working right, it leads

to the more common form of colon cancer, the kind of cancer we see in people with no family history," Markowitz said.

When the gene is working properly, it keeps genetic material in colon cells from being damaged, he said. The gene monitors DNA, and like a spell-checker in a computer, fixes genetic material that is beginning to break down before it is completely damaged. That keeps the cell from reproducing out of control, which is cancer.

When the hMLH1 gene becomes defective and stops working, the study reports, a naturally occurring chemical called methylation coats DNA in colon cells and they reproduce wildly.

"Cancer is like a ball rolling down a hill," Markowitz said. "It takes time for all the things that have to go wrong to cause the cancer to happen. If you're born with a bad version of this gene,

then from the day you're born, the ball was rolling down the hill and 30 years later, you have cancer. On the other hand, some people are born and the gene is fine, but somewhere in life [the gene becomes faulty and shuts down.] Now their ball is rolling."

The study found that an experimental drug called 5-azacytidine strips the methylation off the DNA, making a cancerous cell more vulnerable to chemotherapy. The research suggests the drug would stop precancerous cells from progressing to cancer.

If a drug could switch the hMLH1 gene back on as soon as it begins to shut down, Markowitz said, it could prevent cancer from developing in the first place. The problem is that 5-azacytidine is toxic — it kills large numbers of disease-fighting white blood cells.

"A little bit better version of this drug would probably be ac-

ceptable to give to folks who have cancer to try to treat the cancer," Markowitz said. The University Hospitals/CWRU researchers are looking for pharmaceutical companies willing to develop a safer drug.

The researchers also hope to develop a blood test to detect defective or shut-down hMLH1 genes, thus acting as a cancer predictor. They are seeking donor blood from people who have a family history of colon cancer. Those interested in participating may call (216) 844-5432.

Markowitz is heartened by the findings, but does not want to give patients false hope.

"I don't want somebody that is suffering from cancer right now to have the impression that if they call me, I have a magic bullet for them, because we don't yet," he said. "But I would like people to know that there is hope, that we do better colon cancer treating now than we did 5 years ago."