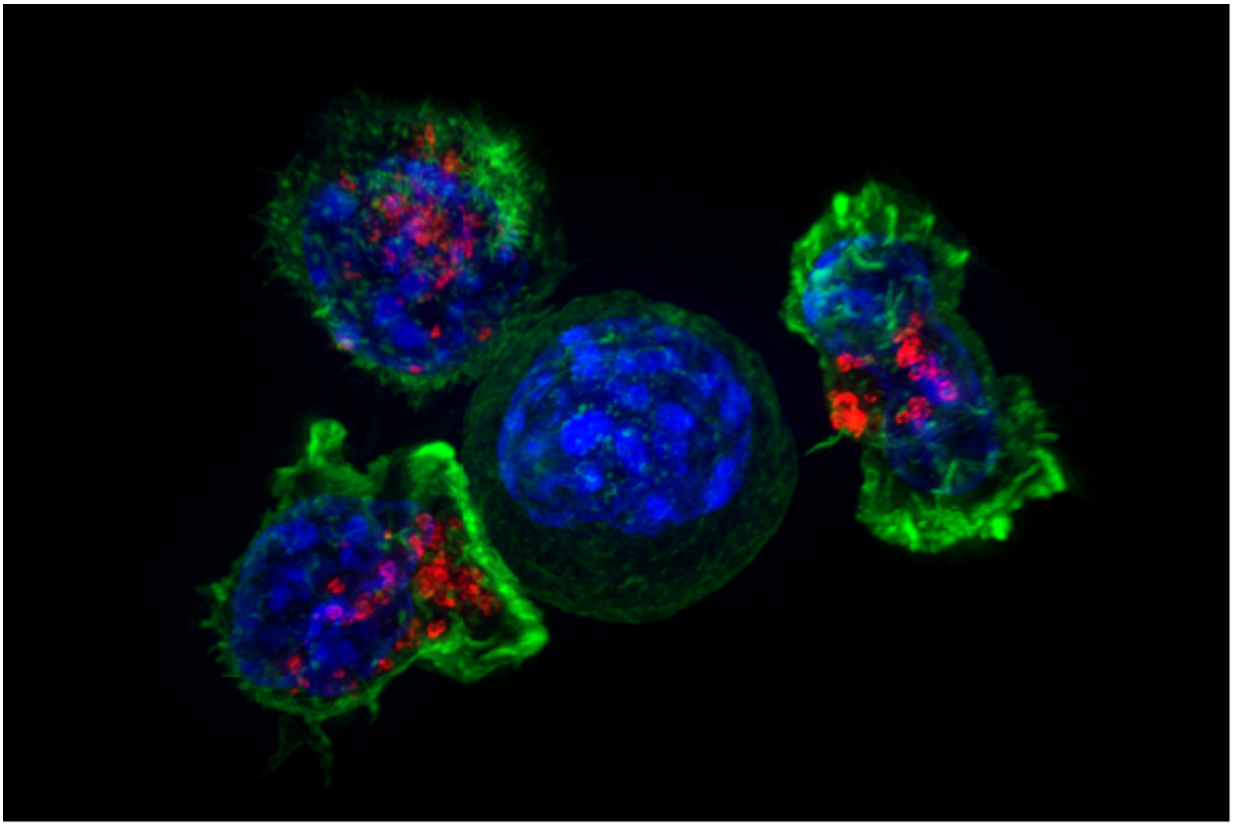
Discovery of colon cancer pathway could lead to new targeted treatments

February 25 2019, by Guodong Zhang



Killer T cells surround a cancer cell. Credit: NIH

University of Massachusetts Amherst food science researchers have pinpointed a set of enzymes involved in tumor growth that could be targeted to prevent or treat colon cancer.

"We think this is a very interesting discovery," says Guodong Zhang, assistant professor of food science, whose study was published in the journal *Cancer Research*. "Our research identifies a novel therapeutic target and could help to develop novel strategies to reduce the risks of colon cancer."

Colon cancer is the third most common cancer and the second leading cause of cancer-related death in the United States, according to the Centers for Disease Control and Prevention, claiming some 50,000 lives each year. Those statistics emphasize the need to discover new cellular targets that are crucial in the development of colon cancer, Zhang says.

In their study, UMass Amherst researchers tested their hypothesis that once present, colon cancer was increased by enzymes known as cytochrome P450 (CYP) monooxygenases and the fatty acid metabolites they form, epoxyoctadecenoic acids (EpOMEs). The researchers compared healthy mice and mice with colon cancer by performing metabolomics, a comprehensive and complex analysis of metabolites, which are produced when food and chemicals are broken down.

In recent years, metabolomics has emerged as a powerful technology in precision medicine because it can offer a detailed picture of biological processes and molecular phenotypes, or characteristics. Precision medicine tailors treatment to an individual's unique genetic and molecular profile.

As they suspected, the researchers found that certain fatty acid metabolites were more abundant in colon cancer. "If a mouse has colon cancer, the plasma and colon concentrations of EpOMEs are very dramatically increased and the EpOME-producing enzymes, CYP monooxygenases, are overexpressed in the colon," Zhang says.

Researchers also studied human colon cancer cells, comparing them to

normal colon cells, and found the same results: an overexpression, or plethora, of the CYP monooxygenase enzymes.

Next, using pharmacological and genetic approaches, the researchers removed or inhibited the CYP monooxygenase enzymes in mice with colon cancer and found that tumor growth was suppressed. "If you block the enzyme, colon cancer can be significantly reduced," Zhang says.

In an effort to determine which metabolites were involved in the colon cancer-enhancing effects, researchers studied the biological actions of CYP monooxygenase metabolites. In an in vitro test, they found that EpOME, but not other CYP monooxygenase metabolites, increased inflammation in both inflammatory and colon cancer cells. They then treated cancer-induced mice with EpOME and found an increase in the number and size of tumors. "We showed that at a low dose this metabolite can make colon cancer more aggressive," Zhang says.

Taken together, the results of the research demonstrate "that the previously unappreciated CYP monooxygenase pathway" could be explored for preventing or treating colon cancer, Zhang concludes.

He points out that previous studies have shown that some FDA-approved drugs inhibit CYP monooxygenases, including Micardis, a blood pressure medication, and Lopid, which is used to lower cholesterol. "That suggests that these drugs could be repurposed for preventing or treating colon cancer," Zhang says. "And novel monooxygenase inhibitors could be developed for use in humans."

Using data from his groundbreaking research, Zhang has received a $406,000 USDA grant to study how dietary fats may regulate colon cancer. EpOMEs are metabolites of linoleic acid, which are found in vegetable oils and red meat.

"Based on our findings, overconsumption of linoleic acid could increase tissue concentrations of EpOMEs, which have potent effects to exaggerate inflammation and tumor growth in the colon," Zhang says.

More research is needed in animal models, which can be controlled more easily than human studies. "We need to better understand this pathway in colon cancer, which ultimately may help us suggest nutritional and therapeutic approaches to reduce the risks of colon cancer," Zhang says.

More information: *Cancer Research* (2019). DOI: 10.1158/0008-5472.CAN-18-3221 , cancerres.aacrjournals.org/con … 18-3221.article-info

Provided by University of Massachusetts Amherst