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Retinoic acid suppresses colorectal cancer development, study finds

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Retinoic acid, a compound derived in the body from vitamin A, plays a critical role in suppressing colorectal cancer in mice and humans, according to researchers at the Stanford University School of Medicine.

Mice with the cancer have lower-than-normal levels of the metabolite in their gut, the researchers found. Furthermore, colorectal cancer patients whose intestinal tissues express high levels of a protein that degrades retinoic acid tend to fare more poorly than their peers.

The research is the first to unravel a complicated dance between retinoic acid levels, immune-related inflammation and gut microorganisms. It may suggest new ways to prevent or treat colorectal cancer in humans.

"The intestine is constantly bombarded by foreign organisms," said Edgar Engleman, MD, professor of pathology and of medicine. "As a result, its immune system is very complex. There's a clear link in humans between inflammatory bowel disease, including ulcerative colitis, and the eventual development of colorectal cancer. Retinoic acid has been known for years to be involved in suppressing inflammation in the intestine. We wanted to connect the dots and learn whether and how retinoic acid levels directly affect cancer development."

Engleman is the senior author of the research, which will be published online Aug. 30 in *Immunity*. Postdoctoral scholar Nupur Bhattacharya, PhD, and graduate student Robert Yuan share lead authorship of the study.

Tumors in mice

Retinoic acid is essential for many processes of growth and development, but it also degrades quickly when exposed to light. This makes it extremely difficult to accurately detect levels of the metabolite in the body.

The Stanford researchers collaborated with colleagues at the University of California-Berkeley, who devised a way to use a technique called quantitative mass spectrometry to measure the retinoic acid in intestinal tissues of mice treated with one or both of two chemicals: a chemical that causes intestinal inflammation, and a chemical that stimulates the development of colorectal cancer. Mice who received both chemicals develop intestinal tumors within nine to 10 weeks of treatment; those treated with just the first chemical develop intestinal inflammation but not cancers.

Engleman and his colleagues found that the mice that developed colorectal cancer had significantly lower-than-normal levels of retinoic acid in their gut than those whose intestines were inflamed but not cancerous. Further investigation showed the intestinal tissue of the animals with cancer made less of a protein that synthesizes retinoic acid and about four times more of a protein that degrades retinoic acid, leading to a rapid net decrease in levels of the metabolite.

Restoring retinoic acid levels

The researchers then tested whether it was possible to affect the disease progression by bringing the levels of retinoic acid in the tissue back into a more normal range.

"When we increased the amount of retinoic acid in the intestine, either by supplementing the animal with retinoic acid or by blocking the

activity of the degradation enzyme, we were able to dramatically reduce the tumor burden in the animals," said Engleman. "Conversely, inhibiting retinoic acid activity significantly increased the tumor burden."

The researchers next investigated the levels of the synthesis and degradation proteins in stored samples of intestinal tissue obtained from people with either ulcerative colitis or colorectal cancer associated with ulcerative colitis. Because the samples had been stored, rather than freshly collected, it was not possible to directly measure the retinoic acid levels in the human tissues.

The researchers found that, similar to what they had seen in the mice, human colorectal cancer tissue had higher levels of the degradation protein and lower levels of the synthesis protein than were found in tissue that was simply inflamed. Furthermore, they saw an inverse correlation in the amount of degradation protein and how long the patient had lived. In other words, those patients with increased amounts of the degradation enzyme in their intestinal tissue tended to fare more poorly than others with less of the enzyme.

Because the researchers also observed similar changes in protein levels in tissue samples from patients with colorectal cancer but with no prior history of ulcerative colitis, they wondered if there could be another cause of intestinal inflammation that affects retinoic acid levels. They knew that naturally occurring bacteria in the gut can sometimes cause local inflammation and hypothesized that they might contribute to the development of retinoic acid deficiency and colorectal cancer. Depleting these bacteria by treating mice with broad-spectrum antibiotics dramatically reduced tumor formation in several colorectal cancer models and prevented the alteration in retinoic acid metabolism that was seen in mice with colorectal cancer and in the human intestinal tissue.

"We found that bacteria, or molecules produced by bacteria, can cause a massive inflammatory reaction in the gut that directly affects retinoic acid metabolism," said Engleman. "Normally retinoic acid levels are regulated extremely tightly. This discovery could have important implications for the treatment of human colorectal cancer."

Further investigation showed that retinoic acid blocks or slows cancer development by activating a type of immune cell called a CD8 T cell. These T cells then kill off the cancer cells. In mice, lower levels of retinoic acid led to reduced numbers and activation of CD8 T cells in the intestinal tissue and increased the animals' tumor burden, the researchers found.

"It's become very clear through many studies that chronic, smoldering inflammation is a very important risk factor for many types of cancer," said Engleman. "Now that we've shown a role for retinoic acid deficiency in colorectal cancer, we'd like to identify the specific microorganisms that initiate these changes in humans. Ultimately we hope to determine whether our findings could be useful for the prevention or treatment of colorectal cancer."

Provided by Stanford University Medical Center

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