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Licorice compound offers new cancer prevention strategy

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A chemical component of licorice may offer a new approach to preventing colorectal cancer without the adverse side effects of other preventive therapies, Vanderbilt University Medical Center researchers report.

In the study published in the *Journal of Clinical Investigation*, Raymond Harris, M.D., Ming-Zhi Zhang, M.D., and colleagues show that inhibiting the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) - either by treatment with a natural compound found in licorice or by silencing the 11βHSD2 gene - prevents colorectal cancer progression in mice predisposed to the disease.

Colorectal cancer is the second leading cause of cancer deaths in the United States. While prevention is the best approach for reducing colorectal cancer deaths, few medical strategies exist to prevent the disease.

One promising target for chemoprevention is the enzyme cyclooxygenase 2 (COX-2), which promotes colorectal cancer progression via the action of the enzyme's inflammatory products, the prostaglandins. Inhibiting this enzyme - with non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen or with selective COX-2 inhibitors like Vioxx or Celebrex - reduces the number and size of colon polyps in mice and in patients with an inherited predisposition to colon cancer. However, both types of drugs cause serious adverse side effects that limit their utility for chemoprevention.

Harris and Zhang - nephrologists who are also members of the Vanderbilt-Ingram Cancer Center - have been investigating COX-2 regulation in the kidney. They previously found that inhibiting 11βHSD2 in the kidney suppresses COX-2 expression in that organ.

The colon is one of the only other organs (besides the kidney) with high expression of 11βHSD2, suggesting that this enzyme might play a role in colorectal cancer progression.

"Since studies here and elsewhere have shown the importance of COX-2 and colonic carcinogenesis, we postulated that maybe one of the mechanisms by which the normal colon might prevent excessive expression of COX-2 is by 11βHSD2," said Harris, the Ann and Roscoe R. Robinson Professor of Nephrology and director of the division.

The researchers examined expression of 11βHSD2 in human colon polyps and in the colons of mice predisposed to colon cancer. They found that 11βHSD2 was increased in polyps found in both mice and humans and correlated with COX-2 expression and activity.

They then inhibited 11βHSD2 with glycyrrhizic acid, the main sweet-tasting component of licorice, and by silencing the gene for 11βHSD2.

Both treatments inhibited the production of prostaglandin E2 (an inflammatory molecule produced by the COX-2 enzyme) and prevented the development of polyps (adenomas) and tumor growth and metastasis.

Because 11βHSD2 is highly expressed only in kidney and colon, blocking the enzyme produces effects specific to those tissues - unlike NSAIDs, selective COX-2 inhibitors, and steroid treatments that can prevent cancer progression but also cause serious side effects like gastrointestinal irritation, cardiovascular events, and immunosuppression, respectively.

Licorice, Harris noted, has been used as a nutraceutical for thousands of years for ailments ranging from coughs to constipation. But even licorice is not without side effects; long-term consumption can lead to low blood potassium and increases in blood pressure - side effects linked to the inhibition of 11βHSD2.

"These are relatively minor compared to the cardiovascular side effects of COX-2 inhibitors," Harris said. "We didn't see (these side effects) in the mice we treated…but it would be something to be aware of, and something that could easily be treated with a diuretic."

Harris and colleagues are continuing to investigate the mechanism of 11βHSD2 inhibition. Zhang, an assistant professor of Medicine and of Cancer Biology, also plans to look at the enzyme's role in lung cancer and other tumors.

And although this natural chemical is an appealing drug lead in itself, the researchers are also working with the Vanderbilt Institute for Chemical Biology to develop more specific and potent inhibitors of 11βHSD2.

"We think we can make (an inhibitor) that is more specific and has better delivery to the target tissues," Zhang said.

Source: Vanderbilt University Medical Center