

Scientists identify key factor in relationship between diet, inflammation and cancer

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A team of Children's Hospital Oakland Research Institute (CHORI) researchers has found that a category of lipids known as sphingolipids may be an important link in the relationship between diet, inflammation and cancer. In a paper published online this week in the *Journal of Clinical Investigation*, Dr. Julie Saba, MD, PhD and her team provide evidence that a sphingolipid metabolite called sphingosine-1-phosphate (S1P) found in both mammalian food products and generated by normal human cells can contribute to inflammation of the colon, inflammatory bowel disease (IBD) and inflammation-associated colon cancer, whereas soy and plant-type sphingolipids called sphingadienes may protect against these conditions.

A connection between [inflammation](#) and cancer has been recognized for over a hundred years. This connection is particularly evident in colon carcinogenesis, because patients with IBD have a higher incidence of [colon cancer](#) than the general population. There is increasing evidence that inflammation contributes to the earliest stages of carcinogenesis, namely in the process of cell transformation, where the cell acquires many aspects of cancer characteristics. The observation that IBD and colon cancer incidence rise as nations industrialize suggests that changes in diet and nutrition contribute to colitis and colitis-associated colon cancer.

Bioactive sphingolipids play fundamental roles in carcinogenesis via their ability to regulate programmed cell death pathways, stress responses, immunity, and inflammation. The impact of sphingolipid

metabolism is particularly germane in colon cancer, as gut epithelial cells are exposed to sphingolipid metabolites generated by the breakdown of dietary sphingolipids. S1P, the final breakdown product of mammalian sphingolipids, is a pro-inflammatory signaling lipid that promotes cell growth and carcinogenesis. During malignant transformation and colon cancer progression, genetic changes occur in the gut tissues, including an increase in the enzyme that generates S1P and a decrease in S1P lyase (SPL), the enzyme that catalyzes S1P degradation. These changes lead to accumulation of S1P in the gut mucosa.

To explore the impact of S1P accumulation on inflammation and carcinogenesis, the researchers produced a mouse lacking SPL in the gut tissues. They then characterized its responses using a chemical-induced model of colitis-associated colon cancer. Compared to control mice, the mutated mice exhibited more inflammation and a higher incidence of tumors on this regimen. Using a combination of mouse and cell culture experiments, the scientists identified a cascade of steps downstream of S1P that lead eventually to the silencing of two tumor suppressing proteins whose functions are to protect against the formation of cancer.

In contrast to the cancer-promoting effects of S1P, the researchers showed that soy or plant-type sphingolipids called sphingadienes cannot be metabolized to S1P and instead enhance the metabolism of S1P by increasing SPL levels in gut tissues when fed to mice. Further, sphingadiene treatment of mice reduced inflammation, signs of IBD, and the incidence of tumors. Finally, the researchers showed an increase in S1P-related gene expression in the colons of patients with IBD compared to controls.

The research suggests that while mammalian sphingolipids may promote inflammation and carcinogenesis, plant/soy sphingolipids cannot be converted into S1P, are anti-inflammatory and reduce the activity of several cancer signaling pathways. The data suggests that dietary

sphingolipids may enhance or inhibit [colon carcinogenesis](#), depending on their ability to be metabolized to S1P.

The findings reveal a mechanistic link between diet, inflammation and cancer and provide evidence supporting the further investigation of sphingadienes as colon cancer chemopreventive agents in patients at risk, such as children and adults with IBD.

More information: *Journal of Clinical Investigation*,
www.jci.org/articles/view/74188

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