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Gut microbes turn carbs into colorectal cancer

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Colorectal cancer has been linked to carbohydrate-rich western diets, but the underlying mechanisms have been unclear. A study published by Cell Press July 17th in the journal *Cell* shows that gut microbes metabolize carbohydrates in the diet, causing intestinal cells to proliferate and form tumors in mice that are genetically predisposed to colorectal cancer. Treatment with antibiotics or a low-carbohydrate diet significantly reduced tumors in these mice, suggesting that these easy interventions could prevent a common type of colorectal cancer in humans.

"Because hereditary colorectal cancer is associated with aggressive and rapid tumor development, it is critical to understand how major environmental factors such as microbes and diet interact with genetic factors to potentially affect disease progression," says senior study author Alberto Martin of the University of Toronto. "Our study provides novel insights into this question by showing that gut bacteria interact with a carbohydrate-rich diet to stimulate a prevalent type of hereditary colon cancer."

Carbohydrates account for about half of the daily caloric intake of adults on a western-style diet, and previous studies have linked carbohydrate-rich diets to colorectal cancer in humans. This type of cancer is also frequently associated with mutations in a tumor suppressor gene called APC as well as the MSH2 gene, which plays a critical role in repairing DNA damage. However, it has been unclear why mutations affecting the DNA repair pathway are much more common in colorectal cancer compared with other cancers. Because gut microbes also contribute to

the development of colorectal cancer, Martin and his team suspected that they could interact with diet to explain how the mutations could cause this type of cancer.

To explore this question in the new study, Martin and his collaborators used mice that had APC and MSH2 mutations and thus were predisposed to develop colorectal cancer. Treatment with either antibiotics or a low-carbohydrate diet reduced cell proliferation as well as the number of tumors in the small intestines and colons of these mice. These two treatments also reduced levels of certain gut microbes that metabolize carbohydrates to produce a fatty acid called butyrate. When the researchers increased butyrate levels in the antibiotic-treated mice, cell proliferation and the number of tumors increased in the small intestines.

Taken together, the findings suggest that carbohydrate-derived metabolites produced by gut microbes drive abnormal cell proliferation and tumor development in mice genetically predisposed to colorectal cancer. "By providing a direct link between genetics and gut microbes, our findings suggest that a diet reduced in carbohydrates as well as alterations in the intestinal microbial community could be beneficial to those individuals that are genetically predisposed to colorectal cancer," Martin says.

More information: *Cell*, Belcheva et al.: "Gut microbial metabolism drives transformation of Msh2-deficient colon epithelial cells." www.cell.com/cell/abstract/S0092-8674(14)00736-3

Provided by Cell Press