Obesity primes the colon for cancer, study finds

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Obesity, rather than diet, causes changes in the colon that may lead to colorectal cancer, according to a study in mice by the National Institutes of Health. The finding bolsters the recommendation that calorie control and frequent exercise are not only key to a healthy lifestyle, but a strategy to lower the risk for colon cancer, the second leading cause of cancer-related death in the United States.

Paul Wade, Ph.D., and Thomas Eling, Ph.D., scientists at the National Institute of Environmental Health Sciences (NIEHS), part of NIH, led a collaborative team that made the discovery. The study appeared online April 1 in the journal *Cell Metabolism*.

A large body of scientific literature says people who are obese are predisposed to a number of cancers, particularly colorectal cancer, Eling said. To better understand the processes behind this link, he and his colleagues fed two groups of mice a diet in which 60 percent of the calories came from lard. The first group of mice contained a human version of a gene called NAG-1, which has been shown to protect against colon cancer in other rodent studies. The second group lacked the NAG-1 gene.

The NAG-1 mice did not gain weight after eating the high-fat diet, while mice that lacked the NAG-1 gene grew plump.

The researchers noticed another striking difference between the two groups of animals.

"The obese mice exhibited molecular signals in their gut that led to the progression of cancer, but the NAG-1 mice didn't have those same indicators," Eling said.

The researchers looked for molecular clues, by isolating cells from the colons of the mice and analyzing a group of proteins called histones.

Histones package and organize DNA in a cell's nucleus, and sometimes undergo a process known as acetylation, in which chemical tags bind to their surface. The pattern of acetylation varies depending on the chemical processes taking place in the cell.

Wade explained that the acetylation patterns for the obese mice and the thin NAG-1 mice were drastically different. Patterns from the obese mice resembled those from mice with colorectal cancer. The additional weight they carried also seemed to activate more genes that are associated with colorectal cancer progression, suggesting the obese mice are predisposed to colon cancer.

"Any preexisting colon lesions in these animals are more likely to evolve rapidly into malignant tumors," Wade said. "The same thing may happen in humans."

Wade and Eling want to find out exactly how obesity prompts the body to develop colorectal cancer. Wade said that the likely candidates for triggering tumor growth in the colon are fat cells, but there are many more possibilities. Finding these cellular switches may give rise to production of medications to keep people from getting colorectal cancer.

"Once we identify the signaling pathways and understand how the signal is transduced, we may be able to design ways to treat colorectal cancer in obese patients," Wade said.

More information: Li R, Grimm SA, Chrysovergis K, Kosak J, Wang X, Du Y, Burkholder A, Janardhan K, Mav D, Shah R, Eling TE, Wade, PA. 2014. Obesity, rather than diet, drives epigenomic alterations in colonic epithelium resembling cancer progression. *Cell Metab*; DOI: 10.1016/j.cmet.2014.03.012 [Online 1 April 2014].

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