Link between obesity and increased risk of colorectal cancer revealed

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Obesity has long been associated with increased risk of colorectal cancer, but the link has never been understood. Now, a research team led by investigators at Thomas Jefferson University has revealed the biological connection, and in the process, has identified an approved drug that might prevent development of the cancer. Their study is published in *Cancer Research*.

In mice, investigators found that a high caloric diet turned off expression of a key hormone in the intestine, which led to deactivation of a tumor suppressor pathway. Genetic replacement of that hormone turned the tumor suppressor back on and prevented cancer development—even when mice continued to eat excess calories.

These findings position the use of the pill linaclotide (Linzess), which is structurally related to the lost hormone, as a therapeutic approach to preventing colorectal cancer in obese patients, says the study's senior author, Scott Waldman, M.D. Ph.D., Chair of Pharmacology & Experimental Therapeutics at Sidney Kimmel Medical College of Thomas Jefferson University.

The U.S. Food and Drug Administration approved linaclotide in 2012 to treat irritable bowel syndrome with constipation as well as chronic idiopathic constipation (chronic constipation from unknown causes).

"Our study suggests that colorectal cancer can be prevented in obese individuals with use of hormone replacement therapy—much as other

diseases associated with hormone deficiency, such as loss of insulin in diabetes, can be treated," Dr. Waldman says.

"These findings came as a surprise—we and many other researchers worldwide have been trying to disentangle obesity from development of colorectal cancer," he says. "Calories sit in the middle of these two conditions, but the question of what they were doing has been one of the most perplexing and provocative questions in cancer research.

"Now we finally have a big clue as to the origin of colorectal cancer in obese individuals and perhaps in other people as well," says Dr. Waldman, who is also the Samuel MV Hamilton Professor.

The risk of developing colorectal cancer in obese persons is about 50 percent greater, compared to risk in lean people. Scientists had thought the issue was one based on the amount of fat tissue and the associated unknown metabolic processes—excess calories that fuel cell energy and growth—but that did not turn out to be the case here, Dr. Waldman says.

Dr. Waldman is already involved in a multisite clinical study testing dose and side effects of linaclotide use in healthy volunteers. Investigators from the National Cancer Institute, Mayo Clinic, and Fox Chase Cancer Center are participating.

In the present study, the research team—which includes investigators from Harvard and Duke Medical Schools—used genetically engineered mice on different diets to conduct their investigation.

They found that obesity (either from excess fat or carbohydrate consumption, or both) is associated with loss of the hormone guanylin, which is produced in the intestine's epithelium—the cells lining the organ. The hormone turns on its receptor, guanylyl cyclase C (GUCY2C), which regulates processes underlying regeneration of the

intestinal epithelium. "The lining of the intestines is very dynamic and continuously being replaced, and GUCY2C contributes to the choreography of the key processes needed for this regeneration," Dr. Waldman says.

Deactivation of the guanylin gene is common in colorectal cancers in both humans and animals, he says. In that regard, morbidly obese patients exhibit an 80 percent decrease in guanylin gene expression compared to lean people, he says.

But in this study, the researchers discovered the consequences of that loss. They found that the guanylin hormone receptor acts as a growth-controlling tumor suppressor, and without the hormone, the receptor is silenced. "This happens extremely early in development of the cancer," Dr. Waldman says. "When the receptor is silenced, the epithelium becomes dysfunctional, setting up the conditions for cancer development."

The scientists checked their findings by creating mice that carried a transgene that won't allow the guanylin gene to be shut off. "Even in the setting of excess calories, from any diet source, tumors don't develop," he says.

Their experiments demonstrated that obese mice, compared to lean mice, were much more likely to silence the hormone and its receptor. "We believe that if colorectal cancer is going to develop, it will be through this silencing mechanism—and that it will happen much more frequently in the obese," Dr. Waldman says. Even so, investigators don't yet know the precise molecular mechanism that turns off hormone production.

"The beauty of our findings is that while we know the hormone is lost in the obese mice, its receptors are just sitting there waiting to be switched

on. And this study demonstrates that if you can prevent hormone loss, you can also prevent tumor development. These findings suggest that a drug like linaclotide, which acts like guanylin, can activate GUCY2C tumor-suppressing receptors to prevent cancer in obese patients," he says.

The researchers also showed that the effect of excess calorie consumption can be reversed via calorie restriction, even in obese mice. "The challenges of lifestyle modification notwithstanding, our observations suggest that calorie restriction can reconstitute guanylin expression," Dr. Waldman says. "This may be an effective strategy to prevent colon cancer in the obese."

More information: *Cancer Research*, dx.doi.org/10.1158/0008-5472.CAN-15-1467

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