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Stronger intestinal barrier may prevent cancer in the rest of the body, new study suggests

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A leaky gut may be the root of some cancers forming in the rest of the body, a new study published online Feb. 21 in *PLoS ONE* by Thomas Jefferson University researchers suggests.

It appears that the hormone receptor guanylyl cyclase C (GC-C)—a previously identified tumor suppressor that exists in the intestinal tract—plays a key role in strengthening the body's intestinal barrier, which helps separate the gut world from the rest of the body, and possibly keeps cancer at bay. Without the receptor, that barrier weakens.

A team led by Scott Waldman, M.D., Ph.D., chair of the Department of Pharmacology and Experimental Therapeutics at Jefferson and director of the Gastrointestinal Cancer Program at Jefferson's Kimmel Cancer Center, discovered in a pre-clinical study that silencing GC-C in mice compromised the integrity of the intestinal barrier. It allowed inflammation to occur and cancer-causing agents to seep out into the body, damaging DNA and forming cancer outside the intestine, including in the liver, lung and lymph nodes.

Conversely, stimulating GC-C in intestines in mice strengthened the intestinal barrier opposing these pathological changes.

A weakened intestinal barrier has been linked to many diseases, like inflammatory bowel disease, asthma and food allergies, but this study

provides fresh evidence that GC-C plays a role in the integrity of the intestine. Strengthening it, the team says, could potentially protect people against inflammation and cancer in the rest of the body.

"If the intestinal barrier breaks down, it becomes a portal for stuff in the outside world to leak into the inside world," said Dr. Waldman. "When these worlds collide, it can cause many diseases, like inflammation and cancer."

The role of GC-C outside the gut has remained largely elusive. Dr. Waldman and his team have previously shown its role as a tumor suppressor and biomarker that reveals occult metastases in lymph nodes. They've used to it better predict cancer risk, and have even shown a possible correlation with obesity.

Reporting in the Journal of Clinical Investigation, Dr. Waldman colleagues found that silencing GC-C affected appetite in mice, disrupting satiation and inducing obesity. Conversely, mice who expressed the hormone receptor knew when to call it quits at mealtime.

However, its role in intestinal barrier integrity, inflammation, and cancer outside the intestine is new territory in the field.

A new drug containing GC-C is now on the verge of hitting the market, but its intended prescribed purpose is to treat constipation.

This study helps lays the groundwork, Dr. Waldman said, for future pre-clinical and clinical studies investigating GC-C's abilities beyond those treatments in humans, including prevention and treatment of inflammatory bowel disease and cancer.

"We've shown that when you pull away GC-C in animals, you disrupt the intestinal barrier, putting them at risk for getting inflammatory bowel

disease and cancer. And when you treat them with hormones that activate GC-C it helps strengthen the integrity of the intestinal barrier," Dr. Waldman said. "Now, if you want to prevent inflammation or cancer in humans, then we need to start thinking about feeding people hormones that activate GC-C to tighten up the barrier."

Provided by Thomas Jefferson University