

# Why Chemotherapy Triggers Nausea—And Other Gut Pain Mysteries

Findings illuminate the mysterious molecular underpinnings of nausea, a common side effect of chemotherapy and other cancer drugs.

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Enteroendocrine cells, which line the wall of the gut, secrete hormones that regulate glucose levels, food intake, and stomach emptying. Abnormal activity of these cells can cause gastrointestinal disorders, such as irritable bowel syndrome (IBS), as well as intestinal tumors.

Damon Runyon Fellow Koki Tohara, PhD, has been investigating the interactions between enteroendocrine cells and the enteric nervous system—the gut-brain axis, in common parlance—in order to identify new treatments for these cancers. But recently, Dr. Tohara and his team made a discovery about the gut-brain axis that sheds light on an all-too-common facet of an existing cancer treatment: the sensation of nausea experienced by patients receiving chemotherapy.

The team homed in on two types of enteroendocrine cells that detect noxious stimuli and send pain signals to the brain. One, called villus EC cells, are located higher in the gut lining; they are the first to detect a harmful stressor, like a metabolized chemotherapy drug. They respond by releasing serotonin into the gut, which, in turn, activates nerve pathways that send pain signals to the brain. Deeper in the gut are crypt EC cells, which secrete hormones to aid digestion. But when they are exposed to harmful stimuli or inflammatory conditions, they too flood the gut with serotonin, maintaining the active pain pathways. With both these types of EC cells activated, pain signals can reverberate through the body long after the initial trigger is gone.

The team's findings illuminate the mysterious molecular underpinnings of nausea, a common side effect of chemotherapy and other cancer drugs that can negatively affect a patient's quality of life and ability to tolerate cancer treatment, and more broadly shed light on the chronic pain associated with conditions like IBS.

"We now have a much clearer picture of how gut pain is generated and maintained," said Stuart M. Brierley, a lead author of the study. "If we can find ways to regulate how EC cells are activated, it could be instrumental in finding more effective treatments for chronic gut pain, which affects millions of people around the world."

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