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Gastric cancer fueled by 'crosstalk' between nerves and cancer cells

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Gastric tumors are started by specialized cells in the stomach that signal nerves to make more acetylcholine, according to a study in mice. The multinational team of researchers who conducted the study also identified a substance called nerve growth factor that stimulates nerve development and, when blocked, inhibits stomach cancer development.

The findings were published today in *Cancer Cell*.

Previous studies have shown that nerves are abundant in the gastric tumor microenvironment. In an earlier paper, the researchers demonstrated that inhibiting signaling by the neurotransmitter acetylcholine, by severing the vagus nerve in the stomach or treating with Botulinum toxin, shrank or prevented the growth of gastric tumors in mouse models.

"Nerves and acetylcholine clearly play a key role in regulating the development and growth of cancer cells, particularly cancer stem cells, in the gastric tumor microenvironment," said Timothy C. Wang, MD, the Dorothy L. and Daniel H. Silberberg Professor of Medicine at Columbia University Medical Center (CUMC) and senior author of the paper. "But little is known about what is driving cancer in the earliest stage of development, before the expansion of nerves in the microenvironment. We also wanted to find out where acetylcholine is coming from before the growth of nerves."

Through a series of experiments in mouse models, the researchers

determined that a neurotrophin (substance that triggers nerve growth) called nerve growth factor is highly expressed in gastric cancer cells. They also discovered that tuft cells—specialized cells found in the lining of the digestive tract that, like nerves, communicate with other cells—provide another source of acetylcholine for cancer cell growth, particularly during the formation of tumors.

"We learned that tuft cells are increased during the earliest stage of gastric tumor development, making acetylcholine and stimulating the production of nerve growth factor within the lining of the stomach," said Dr. Wang. "As nerves grow in around the tumor, tuft cells decrease."

In additional experiments, the scientists showed that overexpression of nerve growth factor in the mouse stomach drove tumorigenesis. Furthermore, administration of a nerve growth factor receptor inhibitor prevented stomach cancer in the mice.

"Our study provides some insight into the cellular crosstalk that leads to the development of stomach cancer, and points to a viable therapeutic target for this type of cancer," said Dr. Wang. "Using our findings as a paradigm, additional studies can be done to identify the specific neurotrophins and neurotransmitters that are involved in tumor development in other areas of the body."

The study is titled, "Nerve growth factor promotes gastric tumorigenesis through aberrant cholinergic signaling."

Provided by Columbia University Medical Center