Researchers investigate possible colon cancer risk for new generation of weight-loss drugs

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Gastric bypass and similar stomach-shrinking surgeries are a popular option for obese patients looking to lose weight or treat type 2 diabetes. While the surgeries have been linked to a decreased risk in many types of cancers, the single outlier in a 2013 long-term study of 77,000 obese patients was colon cancer. In the March 3 issue of the journal *Cell Metabolism*, scientists at Mount Sinai Hospital in Toronto present work in mice that could explain this association and raise safety concerns for a new generation of weight-loss drugs that mimic the biological after effects of these procedures.

Gut hormones and bile acids aid in digestion, but some, such as glucagon-like peptide-2 (GLP-2), are also gut growth factors, which stimulate cell division in the intestines. In the *Cell Metabolism* paper, researchers identify a new gut-growth role for another gut hormone, glucagon-like peptide-1 (GLP-1). Using genetic tools to dissect how the molecule affects cells in the intestine, they demonstrate that increasing the activity of GLP-1, or eliminating its action by deleting the GLP-1 receptor, can increase or decrease the incidence of intestinal tumors in mice.

"For many years, people focused on GLP-1 as a beta cell growth factor, and some investigators raised questions about the possibility of pancreatic cancer," says senior author Daniel Drucker, MD, an endocrinologist at Mount Sinai Hospital's Lunenfeld-Tanenbaum Research Institute and a Professor of Medicine at the University of Toronto.

"We don't have any evidence that that's the case; however, our paper now raises the possibility that GLP-1 is an intestinal growth factor."

"No previous studies to date have linked long-term use of GLP-1-based drugs with increased rates of cancer; however, we think patients with a previous history, or increased risk, of colon cancer may not be ideally suited for these therapies," he adds.

Based on the mouse data, Dr. Drucker is also raising questions about the long-term safety of new investigational drugs in clinical development for diabetes and other metabolic diseases, which elevate GLP-1, GLP-2, and bile acids. For example, drugs targeting the glucagon receptor may potentially lead to increased circulating levels of GLP-1, GLP-2, and bile acids, depending on the dose and duration of treatment.

"We're pretty conservative about not overstating the potential clinical relevance of our studies done in mice, but mouse data always generate a hypothesis, and my hypothesis would be that if you have increased levels of gut-growth molecules, I would consider following up with regular colonoscopies for the appropriate patients," Dr. Drucker says.

More information: *Cell Metabolism*, Koehler et al.: "GLP-1R Agonists Promote Normal and Neoplastic Intestinal Growth through Mechanisms Requiring Fgf7" www.cell.com/cell-metabolism/a … 1550-4131(15)00057-1

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