Bile - not acid - is bad guy in triggering precancerous condition associated with reflux disease

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For many people with gastroesophageal reflux disease or GERD, acid reflux drugs are the answer to their woes, curbing the chronic heartburn and regurgitation of food or sour liquid characteristic of the disorder. But when it comes to Barrett's esophagus, a condition commonly found in people with GERD, acid control may be less important than beating back another bodily fluid – bile.

A new study published in the *Annals of Surgery* shows that bile – a digestive fluid that leaks backwards from the stomach into the esophagus along with acid in patients with GERD – plays a critical and previously unrecognized role in the development of Barrett's esophagus. Study authors say the findings provide new avenues for the prevention and treatment of the condition, which is the only known cause of a rare but often deadly type of cancer called esophageal adenocarcinoma.

"Our ultimate goal is to understand the biology of Barrett's so that we may find drugs that inhibit or reverse the condition, thus preventing cancer," said lead study author Jeffrey H. Peters, M.D., an internationally recognized expert in surgery of the esophagus and stomach and the Seymour I. Schwartz Professor and Chair of the Department of Surgery at the University of Rochester Medical Center. "The finding that bile is important is key because current drug therapies for GERD focus largely on acid control."

Acid-reducing drugs called proton pump inhibitors or PPIs are some of the most popular and best-selling drugs in America according to IMS Health, an organization that tracks pharmacy data. While the drugs do a great job of masking GERD symptoms by neutralizing stomach acid, Peters' research suggests they may not be the answer when it comes to blocking Barrett's esophagus. Other research even indicates that such drugs may actually make patients more prone to developing Barrett's.

Normally, our esophagus – the muscular tube connecting the mouth to the stomach – is lined with skin-like tissue. But, in people with Barrett's, it's replaced by tissue that more closely resembles the lining of our intestine, which is smooth and red. Peters' team found that bile that washes up from the stomach into the esophagus shuts off genes responsible for the normal, skin-like lining of the organ, and turns on genes that produce the intestine-like lining that is the hallmark of Barrett's.

They discovered that acid, on the other hand, didn't largely influence the change from one cell type to another.

While previous research established that reflux components encouraged the development of intestinal tissue in the esophagus that alone was never enough to produce the changes that led to Barrett's.

"The main leap this study makes is that normal esophageal cell growth must be turned off and intestinal cell growth must be turned on in order for the disease to take hold," noted Peters, who is president elect of the International Society of Diseases of the Esophagus. "We found that bile promotes both processes."

Study author Tony E. Godfrey, Ph.D., says the findings make perfectly good sense. "In people with Barrett's, the inside of the esophagus looks like the inside of the intestine. Bile is normally found in the intestinal

environment, so when stem cells in the esophagus are exposed to bile that is what they change to."

According to Godfrey, a research associate professor in the Department of Surgery, the lining of the esophagus is shed and replaced on a regular basis, so blocking bile's ability to thwart the production of normal esophageal cells may be one potential treatment strategy. Currently, the only way to stop all reflux components, including bile, is to surgically reconstruct the faulty barrier between the esophagus and the stomach.

The team performed the first-ever analysis of all genes that are turned on and off in normal esophageal cells exposed chronically to bile or acid. The findings were tested and confirmed in human samples of normal esophageal cells and in cells from patients with Barrett's esophagus.

The research is especially exciting for Peters, who regularly treats patients with Barrett's as well as patients who develop esophageal adenocarcinoma. Though uncommon, Peters says it's one of the fastest-rising cancers in the world, likely due to the increase in obesity, which triggers reflux disease and Barrett's. Unfortunately, it is an extremely aggressive cancer that is usually caught at a very late stage, so prevention strategies are greatly needed.

Provided by University of Rochester Medical Center