Researchers identify new heartburn target

May 9 2017, by Morgan Sherburne

Acid reflux and heartburn affect more than 20 percent of the U.S. population, but common medications to treat the disease might not work for a large portion people who suffer from the diseases.

In a new study, University of Michigan researchers have identified a pathway in the cells of the stomach lining that could be a promising target for new drugs to treat the disease.

When we eat, histamine, which regulates function in the gut, binds with a receptor on the epithelial cells—or cells lining the inside of the stomach. When histamine does this, it nudges an ion channel protein called TRPML1 to trigger a calcium pathway.

The calcium pathway triggers the movement of yet another key protein called proton pumps, said lead researcher Haoxing Xu, U-M professor of molecular, cellular and developmental biology. When the proton pump is activated, it secretes acid into the stomach, which breaks down food into digestible components.

When this calcium pathway isn't working correctly, it can produce too little acid. Acid deficiency leads to atrophy in the stomach and, potentially in the long term, stomach cancer. When the pathway overproduces acid, it leads to acid reflux.

Previous generations of medications to treat acid reflux disease either target histamine receptor or the proton pump. Antacid medications that target histamine dampens the message to the proton pump to release

acid. Antacids that target the proton pump block the production of acid from the pump itself.

But these medications don't work for 20 percent of the population with acid reflux disease, according to the International Foundation for Functional Gastrointestinal Disorders. For these people, the protein Xu's team studied could provide a new target for drugs.

"We don't know whether we might be able to provide a new generation of antacid drug, but clearly there is some problem if there are 20 percent of people who are resistant to older versions of these medications," Xu said. "For them, this pathway could be an option."

To test whether the protein was crucial to helping proton pumps produce acid, Xu's team examined that pathway in several ways. First, they used a mouse with that pathway genetically knocked out, and the mouse produced no acid. Second, they used a high throughput screening to find small molecules that would activate or inhibit the channels.

Activating the channels with these small molecules led to an increased production of acid in the stomach while inhibiting the channels led to blocking the production of acid in the stomach. This proves, according to Xu, that interfering with the protein TRPML1 affects how the stomach produces acid.

"This is all that biomedical research is: It's not one protein doing the entire job. It's step by step," Xu said. "Each time we figure out one important step, we may figure out a drug to attack it."

The study is published in the journal *Developmental Cell*.

More information: Nirakar Sahoo et al. Gastric Acid Secretion from Parietal Cells Is Mediated by a Ca 2+Efflux Channel in the

Tubulovesicle, *Developmental Cell* (2017). DOI: 10.1016/j.devcel.2017.04.003