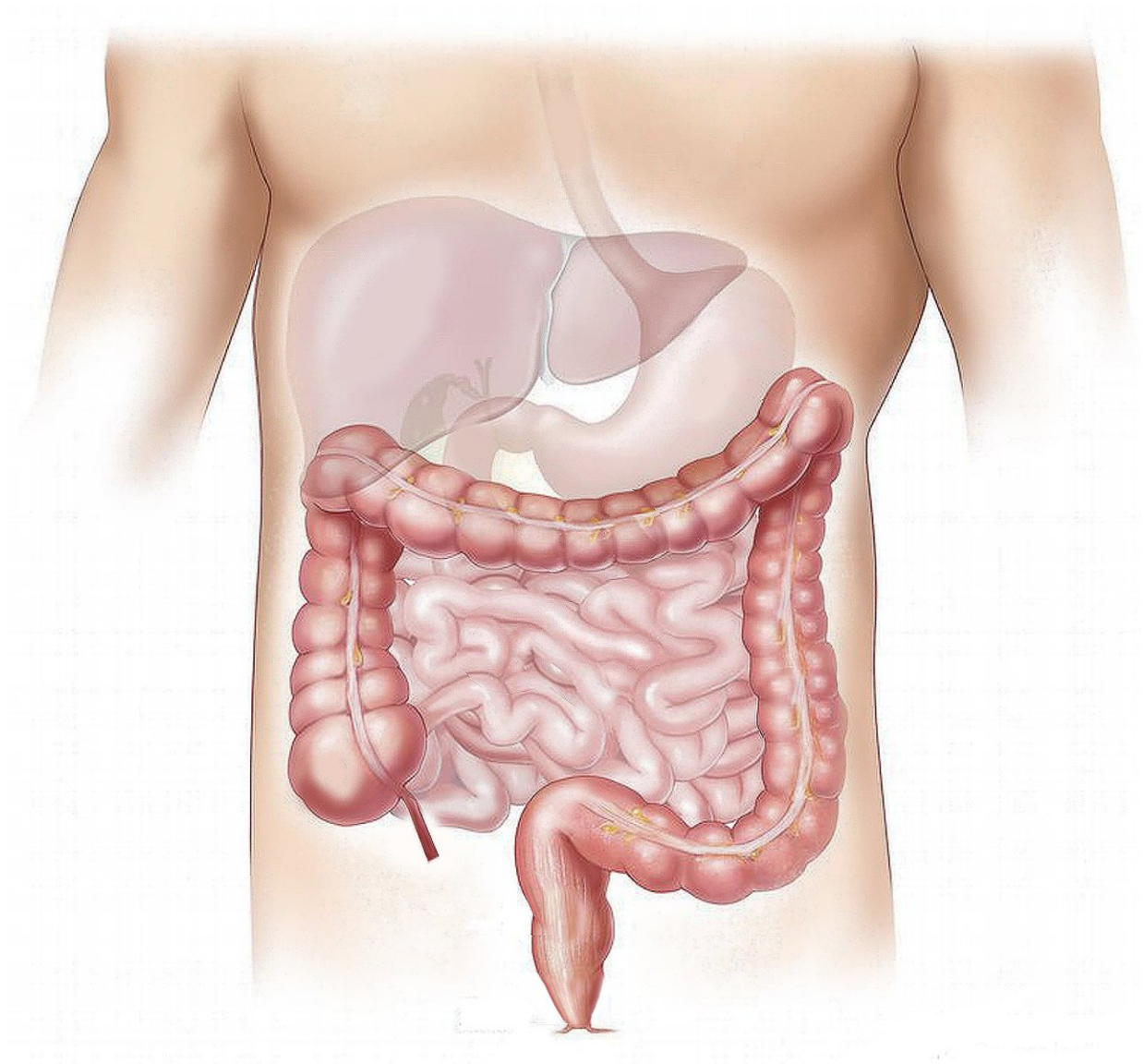
# Betrayed by bile: bile acids help norovirus sneak into cells

December 31 2019



Credit: CC0 Public Domain

A new study led by researchers at Baylor College of Medicine and published in the *Proceedings of the National Academy of Sciences* reveals that human noroviruses, the leading viral cause of foodborne illness and acute diarrhea around the world, infect cells of the small intestine by piggybacking on a normal cellular process called endocytosis that cells use to acquire materials from their environment.

The study found that two compounds present in bile—bile acids and the fat ceramide—are necessary for successful viral infection of a laboratory model of the human small intestine. In addition, the researchers report for the first time that bile acids also stimulate endocytosis in the small intestine. The findings support further exploration of the possibility of reducing norovirus infection by modulating the levels of bile acids and/or ceramide.

"Human noroviruses invade cells of the small intestine where they replicate and cause gastrointestinal problems," said co-first author Victoria R. Tenge, graduate student of molecular virology and microbiology in Dr. Mary Estes's laboratory. "Previous work from our lab showed that certain strains of norovirus required bile, a yellowish fluid produced by the liver that helps digest fats in the small intestine. In the current study, we investigated which bile components were involved in promoting norovirus infection."

The researchers worked with human enteroids, a laboratory model of human intestinal cells that retains properties of the small intestine and is physiologically active.

"Mini-guts, as we call them, closely represent actual small intestine tissue, and, importantly, they support norovirus growth, allowing researchers to study how this virus causes disease," said co-first author

Dr. Umesh Karandikar, a research scientist in the Estes lab.

## Creating a stage that favors viral infection

The researchers discovered that bile acids and ceramide in bile were necessary for viral infection.

"Interestingly, we also discovered that bile acids stimulated the process of endocytosis in mini-guts. Our findings led us to propose that as bile acids activate endocytosis, they create a stage that norovirus takes advantage of by riding along with it to enter the cells and subsequently replicate, causing disease," said corresponding author, Dr. Mary K. Estes, Cullen Foundation Endowed Professor Chair of Human and Molecular Virology at Baylor College of Medicine and emeritus founding director of the Texas Medical Center Digestive Diseases Center. "Bile acid-induced endocytosis in the small intestine was not previously appreciated."

"This strategy works well for a food-borne virus," said co-first author Dr. Kosuke Murakami, who was working in the Estes lab during most of this project. He is currently at the National Institute of Infectious Diseases in Tokyo. "As people ingest food, the body's normal response is to secrete bile into the small intestine. Noroviruses contaminating food piggyback on this natural bodily response to invade cells in the small intestine, replicate and cause disease."

Working with mini-guts not only showed new insights into how norovirus causes disease, but also illuminated details about the basic biological process of endocytosis in the small intestine that had not been reported before.

"Our findings suggest the possibility that modulating the amount of bile acids and/or ceramide could help reduce norovirus infection," Tenge

said.

"This strategy might be particularly helpful to people who have norovirus infections for months, even years," Karandikar said.

**More information:** Kosuke Murakami el al., "Bile acids and ceramide overcome the entry restriction for GII.3 human norovirus replication in human intestinal enteroids," *PNAS* (2019). www.pnas.org/cgi/doi/10.1073/pnas.1910138117

Provided by Baylor College of Medicine