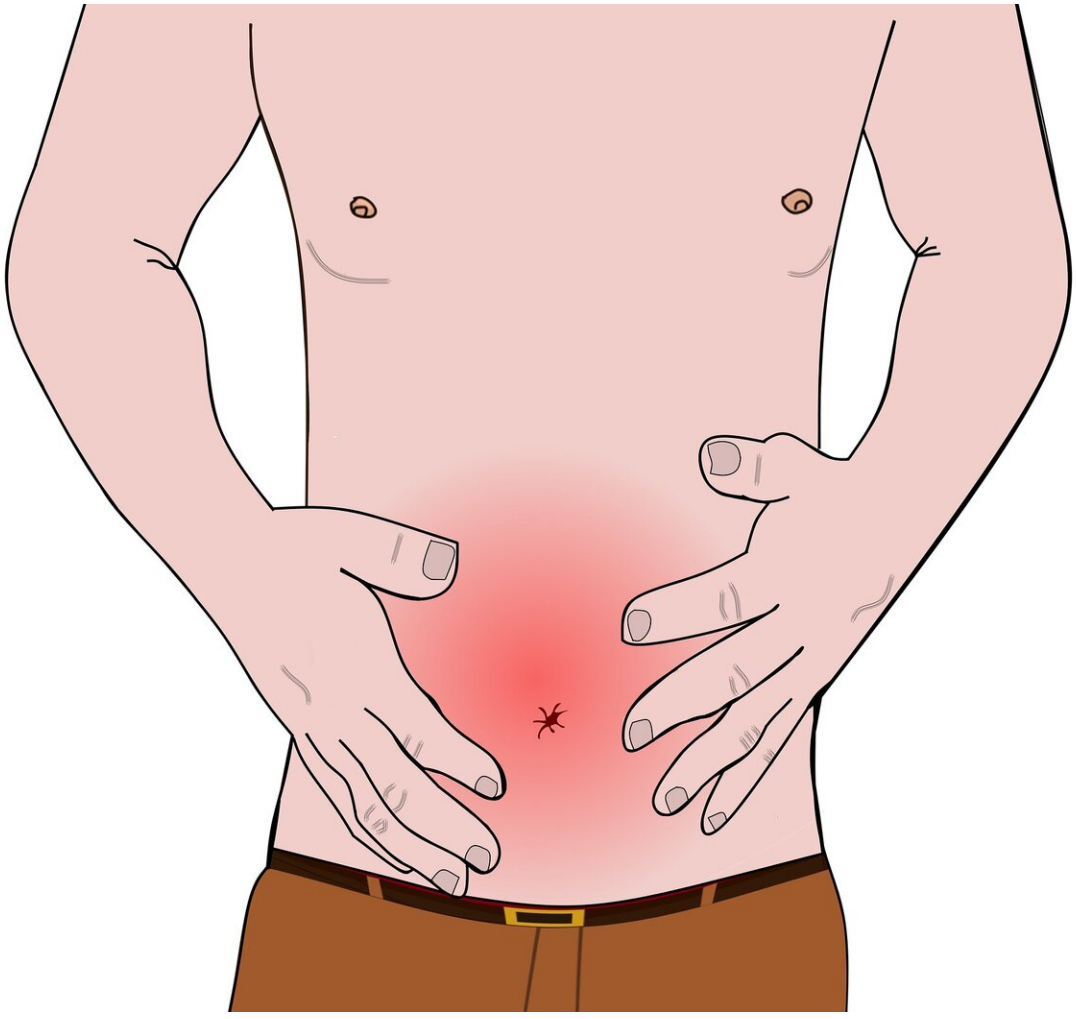
A new mechanism by which rotavirus makes you sick

December 11 2023



Credit: CC0 Public Domain

Rotavirus causes gastroenteritis, a condition that includes diarrhea, deficient nutrient absorption and weight loss. Severe cases result in approximately 128,000 deaths annually in infants and children worldwide. Despite intense research on how rotavirus causes diarrhea, there is still no complete answer, but in this new study researchers at Baylor College of Medicine report a new mechanism by which rotavirus induces diarrhea, interfering with the normal absorption of nutrients in the intestine.

The study, published in *Proceedings of the National Academy of Sciences*, is the first to show that rotavirus-altered lipid metabolism in the intestine plays a role in the disease. Rotavirus infection leads to the degradation of DGAT1, an enzyme involved in normal lipid droplet formation in intestinal cells, which in turn reduces the production of key nutrient transporters and other proteins required for normal intestinal nutrient absorption, leading to diarrhea.

"We wanted to better understand how rotavirus exploits cellular processes to replicate," said co-corresponding author Dr. Sue E. Crawford, assistant professor of molecular virology and microbiology at Baylor.

"We used the well-established monkey kidney cell (MA104) model of rotavirus infection as well as human intestinal enteroids (HIEs) for these studies. HIEs have revolutionized the study of gastrointestinal (GI) viruses like rotavirus. These multicellular, non-transformed cell cultures retain host genetic properties, cellular organization and recapitulate the function of the human gastrointestinal epithelium. They serve as biologically relevant model systems for studying human GI infections."

"We knew that rotavirus triggers the formation of more lipid droplets than normal in the cells it infects, as it turns the lipid droplets into virus factories. While we were studying this process, we discovered that

rotavirus binds to and breaks down or degrades DGAT1, an enzyme that contributes to the formation of the lipid droplets," Crawford said.

As the researchers looked deeper into DGAT1, they discovered that there are children who are born with mutations in DGAT1 that render the enzyme nonfunctional. "These children have severe chronic diarrhea, which sometimes is fatal," said co-first author, Hunter Smith, graduate student in Dr. Mary Estes' and Crawford's lab at Baylor. "This led us to think that rotavirus-mediated degradation of DGAT1 could be a mechanism by which the virus induces diarrhea."

It was always thought that the virus caused diarrhea by infecting the intestinal cells that take up nutrients, killing them and consequently disrupting the nutrient absorption mechanisms of the intestine.

"But we found a new mechanism by which rotavirus induces diarrhea. Like the children who have a genetic DGAT1 deficiency that causes diarrhea, when rotavirus degrades DGAT1 the result is reduced production of the enzymes that are involved in degrading the food we eat and disruption of the mechanisms that transport nutrients into cells, which leads to diarrhea," Smith said.

"It was very unexpected that rotavirus has a protein that interacts with and degrades DGAT1 and that eliminating DGAT1 would lead to all these downstream effects that would cause diarrhea," Crawford said.

Mutations on DGAT1 in children and the link to diarrhea have been known in the last 10 years. "Before that nobody would have said that there was any association between problems with this enzyme and diarrhea," said Estes, Distinguished Service Professor of Molecular Virology and Microbiology and Cullen Foundation Endowed Chair at Baylor. She also is a member of Baylor's Dan L Duncan Comprehensive Cancer Center and co-corresponding author of this work with Crawford.

"It was very surprising that a rotavirus protein that until now was only known to be important for the virus to replicate, also plays a role in causing diarrhea, a major component of the disease. The fact that it's not a capsid protein or part of the structure that envelops the genetic material of the virus, as we usually would think, tells us that we should not assume that nonstructural proteins do not play roles in causing disease."

Co-first author Zheng Liu, Jeanette M. Criglar, Antonio J. Valentin, Umesh Karandikar and Xi-Lei Zeng also contributed to this work. The authors are affiliated with Baylor College of Medicine or Rice University.

More information: Zheng Liu et al, Rotavirus-mediated DGAT1 degradation: A pathophysiological mechanism of viral-induced malabsorptive diarrhea, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2302161120. doi.org/10.1073/pnas.2302161120

Provided by Baylor College of Medicine