It takes cellular teamwork to heal the intestine

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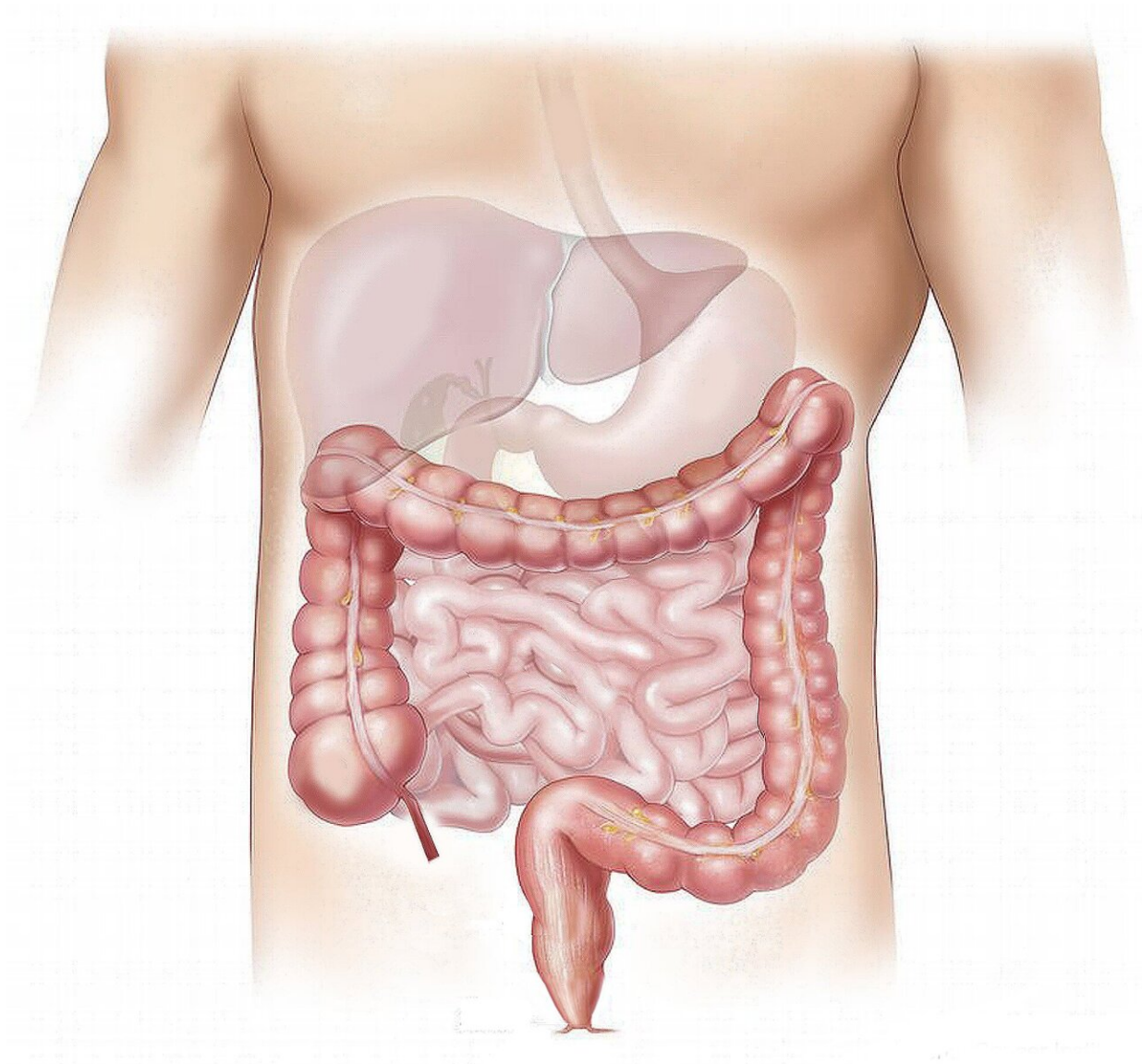

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Researchers at Baylor College of Medicine have uncovered a more detailed picture of how the intestinal epithelium—the lining of the intestines—heals itself after infection with rotavirus. A meticulous single-cell analytical approach to study the repair process in an animal model revealed that the damaged epithelium contains a variety of cell types involved in repairing it through broad coordinated responses that ultimately heal the damaged tissue.

The researchers also unexpectedly discovered that, in addition to enterocytes, which are the cell type typically infected by rotavirus, tuft cells, another cell type in the intestinal epithelium, also are infected and may contribute to the repair response of the epithelium following damage. The findings, published in the *Proceedings of the National Academy of Sciences*, not only provide a better understanding of the healing process following rotavirus infection, but also may contribute new clues about how the virus causes disease.

"Diseases of the digestive tract affect about 60 million Americans each year. These conditions often are associated with damage to the epithelium, which compromises its functions, including digestion of food and absorption of nutrients, and affects overall health," said co-corresponding author Dr. Sarah Blutt, associate professor of molecular virology and microbiology at Baylor.

The researchers' goal on this project was to contribute a better understanding of the repair process following damage to the intestinal epithelium caused by rotavirus in a mouse model. This virus causes approximately 179 million cases of acute gastroenteritis and about 128,000 deaths annually, particularly in children. Getting into the details of the cellular response to the damage resulting from the infection can lead to improved therapies.

Intestinal healing requires teamwork

The internal surface of the intestines is lined with a layer of epithelial cells that folds multiple times, forming many thin, finger-like projections called villi, with crypts between them. Rotavirus infects and kills enterocyte cells residing at the tips of the villi.

"We know that the damage at the tip is quickly communicated to stem cells residing at the crypt, stimulating them to divide and develop into the specialized cells needed to repair the injury at the tip of the villi," Blutt said.

To get a closer look at how the epithelium heals, the team applied a fairly new technology, single-cell transcriptomics, to determine which genes were expressed at the single-cell level in all the cells between the tip and the crypt. There are many different types of cells along the villi, including tuft cells, goblet cells, enterocytes and stem cells, each with specific functions.

"Our analyses revealed a complex cellular landscape characterized by clusters of cells with specific transcriptomic profiles that depended not only on the cell type but also on the cell's location along the villi," said first author Carolyn Bomidi, senior research assistant in the Dr. Mary Estes lab at Baylor. "For example, the same cell type found in different locations may have different transcriptomic profiles."

The researchers' findings also support a new picture of how regeneration happens. They found that, in response to the damage at the tips, subsets of stem cells at the crypt divided more frequently and developed into numerous immature enterocytes that migrated to the tip of the villi to replace those injured by rotavirus.

An unexpected host for rotavirus

Blutt, Bomidi and their colleagues were surprised to find rotavirus genetic material inside tuft cells, a cell type not previously reported to support rotavirus infection.

"The fact that we can detect the virus at all is exciting, given that tuft cells are rare in the intestinal epithelium," Bomidi said. "Rotavirus-infected tuft cells increased the expression of specific genes, including immune response genes, indicating that they are capable of mounting an antiviral response and contribute to the process following an infection."

Altogether, the findings provide evidence that rotavirus infection stimulates a repair program driven by stem cells with involvement of tuft cells that results in the production of immature enterocytes that repair the damaged epithelium.

"I am most excited about this being the first report of the characterization of single-cell transcripts following an intestinal human viral infection," Blutt said. "We consider this a valuable resource of information for researchers involved in gastrointestinal research, to see how each individual cell type responds in the context of a viral infection."

"I anticipate that this approach also will provide new tools to investigate unanswered aspects of how rotavirus and other infectious or inflammatory conditions cause disease," said co-corresponding author Dr. Mary Estes, Cullen Chair and professor of molecular virology and microbiology at Baylor.

Other contributors to this work include Matthew Robertson and Cristian Coarfa, both at Baylor College of Medicine.

More information: Carolyn Bomidi et al, Single-cell sequencing of rotavirus-infected intestinal epithelium reveals cell-type specific

epithelial repair and tuft cell infection, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2112814118