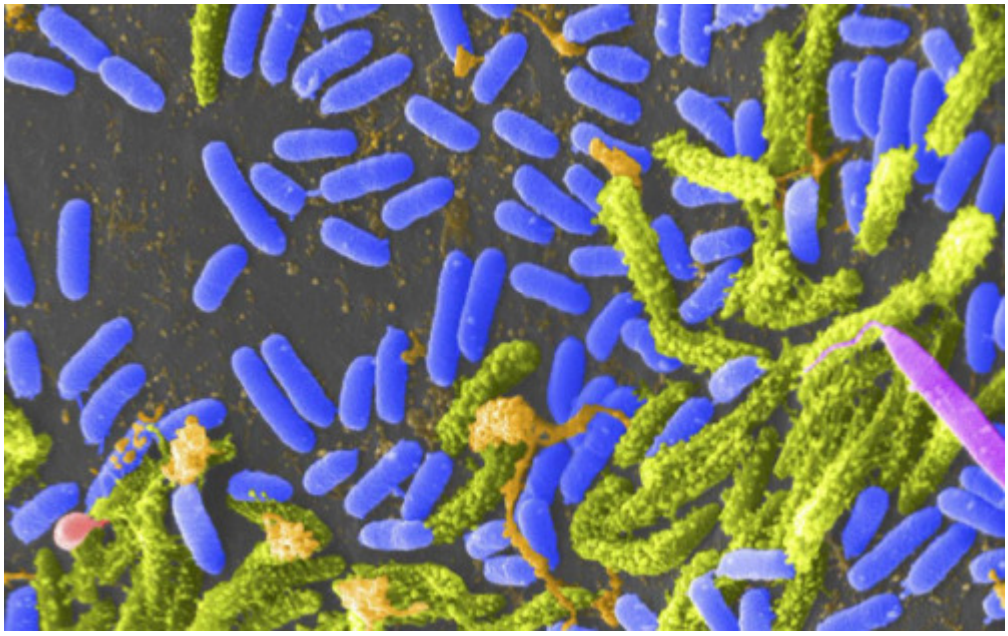
5 years ago
#science
#medicine
#cholera
#diarrhea
#gastroenterology
#public health

Why Humans Get Diarrhea and Other Mammals Don't

As an acute diarrheal disease, cholera is unique to humans. Its human specificity is a major world health problem — cholera affects between 1.4 and 4 million people annually, according to the World Health Organization. A recent report by researchers at the University of California San Diego School of Medicine may finally help explain this specificity — and the role of sialic acids.

The findings are published in the June 18 issue of *PLOS Pathogens*.

All mammalian cells are decorated with sugars called sialic acids. Sialic acids help cells perform many important functions, such as cellular communication and recognition. The two most common types are called Neu5Ac and Neu5Gc, with the latter differing by only a single added oxygen atom. Most mammals make both types of sialic acids; humans produce only Neu5Ac.



Colorized scanning electron micrograph of Vibrio cholera *bacteria (blue). Image courtesy of Tina Carvalho, University of Hawaii at Manoa.*

In their new paper, Ajit Varki, MD, Distinguished Professor of Medicine and Cellular and Molecular Medicine, Kim Barrett, PhD, Distinguished Professor of Medicine, and Victor Nizet, PhD, professor of pediatrics and pharmacy, have shown that this difference in sialic acid expression could explain why other animals do not suffer diarrhea when infected by the causative bacterium *Vibrio*

cholerae. Their study found that a bacterial enzyme called neuraminidase (VcN) preferentially cleaves Neu5Ac over Neu5Gc. It uses this specificity to remodel the surface of gut cells to make them better targets for the cholera toxin Ctx. As a result, VcN increases Ctx binding *in vitro* and allows the bacterium to trigger the intestinal cell to secrete fluid. When human cells are fed Neu5Gc, however, they use it to protect themselves from VcN, which prevents Ctx binding. The fact that other mammals naturally express Neu5Gc could help explain why only humans get diarrhea from *V. cholerae* infections.

The most interesting finding, however, was that human-like mice that expressed only Neu5Ac were more susceptible to infection even without exposure to VcN. “This suggests that there is another mechanism for the diarrheal symptoms that is entirely based on the absence of Neu5Gc,” said Varki. “That’s the big question that needs to be studied further.”

The researchers hope that a better understanding of the fundamental mechanisms of cholera infection will help doctors improve treatment and prevention options for patients. “Anything we can do to understand the pathogenesis is going to be helpful in treatment,” said Barrett. Both Varki and Barrett said further investigation could lead to a potential oral prophylactic.

This study was a “great melding of microbiology, physiology and glycobiology,” said Barrett, noting that the diverse team hopes to pursue further collaboration.

- Ariana Remmel

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