Shape matters: The corkscrew twist of H. pylori enables it to 'set up shop' in the stomach

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The bacterium *Helicobacter pylori*, which lives in the human stomach and is associated with ulcers and gastric cancer, is shaped like a corkscrew, or helix. For years researchers have hypothesized that the bacterium's twisty shape is what enables it to survive - and thrive - within the stomach's acid-drenched environment, but until now they have had no proof.

For the first time, researchers at Fred Hutchinson Cancer Research Center have found that, at least when it comes to *H. pylori*'s ability to colonize the stomach, shape indeed matters. Microbiologist Nina Salama, Ph.D., and colleagues report their findings May 28 in *Cell*.

Salama and colleagues are the first to demonstrate that the bug's helical shape helps it set up shop in the protective gelatin-like mucus that coats the stomach. Such bacterial colonization - present in up to half of the world's population - causes chronic inflammation that is linked to a variety of stomach disorders, from chronic gastritis and duodenitis to ulcers and cancer.

"By understanding how the bug colonizes the stomach, we can think about targeting therapy to prevent infection in the first place," said Salama, the paper's corresponding author and an associate member of the Human Biology Division at the Hutchinson Center. The paper's first author, Laura K. Sycuro, Ph.D., conducted this work while a student in

the University of Washington/Fred Hutchinson Cancer Research Center Molecular and Cellular Biology graduate program. She is now a postdoctoral research associate in the Hutchinson Center's Clinical Research Division.

Specifically, the researchers discovered a group of four proteins that are responsible for generating *H. pylori*'s characteristic curvature. Using a mouse model, they found that laboratory-engineered mutant strains of *H. pylori* that are deficient in these proteins fail to twist properly and, consequently, are unable to colonize the stomach.

"Having these mutant strains in hand allowed us to test whether the helical shape is important for *H. pylori* infection, and it is," Salama said. "All of our mutants had trouble colonizing the stomach and were out-competed by normal, helical-shaped bugs." Interestingly and somewhat puzzlingly, the *H. pylori* mutants retained their ability to propel themselves through a thick, mucus-like gel in a petri dish even though they were unable to establish infection in stomach colonization experiments.

The researchers also discovered a novel mechanism by which these proteins drive the organism's shape, in essence acting like wire cutters on a chain-link fence to strategically snip certain sections, or crosslinks, of the bacterium's mesh-like cell wall. "The crosslinks preserve the structural integrity of the bacterial wall, but if certain links are cleaved or relaxed by these proteins, it allows the rod shape to twist into a helix," Salama said.

Mutant forms of *H. pylori* that lack these proteins are misshapen, ranging from rods to crescents, which hampers their ability to bore through or colonize the stomach lining.

"We found that the bacteria that lost their normal shape did not infect

well, and so we know that if we inhibit normal shape we can slash infection rates," Salama said.

Other disease-inducing bacteria that have these proteins include *Vibrio cholerae*, a comma-shaped bug that causes cholera, and the curved to helical rod-shaped *Campylobacter jejuni*, which is the leading cause of bacterial diarrhea in developed countries.

"The fact that we found proteins that act on the cell wall of *H. pylori* that seem to be important for bacterial survival and that these proteins are found in other pathogens with similar shapes makes them a possible drug target for a number of bacterial diseases," she said.

H. pylori is contagious, but its exact transmission route is unknown. While more than 80 percent of those infected will remain asymptomatic, an estimated 10 percent to 15 percent will develop related diseases such as ulcers and/or stomach cancer. About 70 percent of stomach cancers are associated with *H. pylori* infection.

The current treatment for *H. pylori* infection in those diagnosed with peptic ulcers is a combination of proton-pump inhibitors to reduce gastric acid secretion paired with antibiotics to eradicate the bug. The treatment is not always effective, however, due to the prevalence of antibiotic resistance.

"*H. pylori* infection is hard to treat. There are no vaccines. Right now the only treatment is eradication therapy, and we are running out of tricks because of resistance to essentially all current antibiotics," Salama said.

The bug was first characterized in the early 1980s by Australian researchers Barry J. Marshall and Robin Warren, who in 2005 received the Nobel Prize in physiology or medicine for their discovery. Prior to their finding, the prevailing theory was that most stomach ulcers and

gastritis were caused by spicy food or stress.

In addition to helical rods or spirals, bacterial species come in a wide variety of highly conserved shapes that range from spheres and rods to crescents and stars. They can be found on and within animals and plants - and indeed wherever life exists, from deep in the Earth's crust to the oceans and forests - and they play a key role in regulating the environment. In humans, which harbor 10 times more bacterial cells than human cells, bacteria not only cause diseases ranging from strep throat to pneumonia, but they also perform a host of helpful duties, from aiding digestion to making vitamins that the human body alone cannot produce.

"We are a consortium. We depend on them as they depend on us," Salama said.

Provided by Fred Hutchinson Cancer Research Center