War between bacteria and phages benefits humans

September 2 2014

Woman leans over a source of water that is potentially contaminated with cholera bacteria. Credit: Centers for Disease Control and Prevention (CDC)

In the battle between our immune systems and cholera bacteria, humans may have an unknown ally in bacteria-killing viruses known as phages. In a new study, researchers from Tufts University, Massachusetts General Hospital, Partners In Health, Haiti's National Public Health Laboratory, and elsewhere, report that phages can force cholera bacteria to give up their virulence in order to survive. Importantly, the study—published in *eLife*—found that cholera's mutational escape from phage predation occurs during human infection.

First author Kimberley Seed, Ph.D., and corresponding author Andrew Camilli, Ph.D., both of Tufts University School of Medicine, and their co-authors analyzed phage resistance properties and DNA sequences of

cholera bacteria taken from phage-positive stool samples from patients with cholera in Haiti and Bangladesh, two countries where cholera outbreaks are common at present.

They first determined that cholera bacteria from Haiti changed its DNA in order to fight phages. They compared the bacteria from Haiti to bacteria from Bangladesh collected over many years to determine if the changes were happening on multiple occasions in both countries or only in isolated groups or cases.

The research team discovered that across both time and geography, the cholera bacteria mutated during human infection in order to trade their virulence, or ability to persist and make a human sick, for the ability to defend against the phages. Alternatively, in some patients, the cholera bacteria mutated in a more conservative manner to retain virulence, yet sacrificed the ability to grow optimally in the environment. In either scenario, the cholera bacteria appear to have traded something important in order to survive the onslaught from phages.

"This is the first time we have seen cholera bacteria defend themselves from phages while infecting humans. This suggests that these phages are actively working in our favor, first by killing cholera bacteria within the patient, and second, by genetically weakening the bacteria that are shed by the infected patient such that they are less fit to survive in the environment or less able to cause infection in other people," said senior author Andrew Camilli, a Howard Hughes Medical Institute investigator, professor of molecular biology & microbiology at Tufts University School of Medicine, and member of the Molecular Microbiology program faculty at the Sackler School of Graduate Biomedical Sciences at Tufts University.

"This important finding suggests that we may be able to leverage the strength of phages for treating people with cholera or perhaps preventing

cholera in people who may have been recently exposed as an alternative to antibiotics," he continued.

"Seeing this rapid evolutionary change in the cholera bacteria occurring during human infection suggests that the phages are posing a very strong threat. And to observe this in two different continents suggests that this is not a one-time find, but that it may be happening consistently during cholera outbreaks," said first author Seed, now assistant professor of molecular, cellular and developmental biology at University of Michigan. "Additionally, virtually all bacteria can be infected by phages, which are found wherever bacteria are. So this finding with cholera may be the start of a broader understanding of how phages and bacteria evolve."

Previous work by Camilli and Seed, published last year in *Nature*, provided the first evidence that a phage could acquire a wholly functional and adaptive immune system. They observed that the phage could use this acquired immune system to disarm a phage defense system of the cholera bacteria, allowing the phage to ultimately destroy its bacterial host. This study bolstered the concept of using phage to prevent or treat bacterial infections, and extended the idea that phages can be extremely sophisticated bacterial predators. The team is now investigating the details of this particular arms race between phage and bacteria in hopes of better understanding how phage influence cholera outbreaks and how we can further leverage phages to treat or prevent infections.

The World Health Organization reports that there are an estimated three- to five million cases of cholera cases and 100,000 to 120,000 deaths due to cholera each year. This summer, at least 67 people in Ghana have died of cholera while 6,000 others have been infected. In northern Cameroon, there are reports that 200 people have died and many more infected in the last few months. A current outbreak in South Sudan has taken 130

lives out of a total of more than 5,800 cases. In Haiti, since the beginning of the epidemic there (October 2010) and through March of this year, more than 8,500 people have died, out of more than 700,000 reported cases.

More information: Seed K.D., Yen M, Shapiro B.J., Hilaire I.J., Charles R.C., Teng J.E., Ivers L.C., Boncy J, Harris J.B., Camilli A. "Evolutionary consequences of intra-patient phage predation on microbial populations. eLife (August 26, 2014). dx.doi.org/10.7554/eLife.03497

Provided by Tufts University