Salmonella creates environment in human intestines to foster its own growth

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A study led by researchers at UC Davis has found how the bacteria *Salmonella enterica* — a common cause of food poisoning — exploits immune response in the human gut to enhance its own reproductive and transmission success. The strategy gives *Salmonella* a growth advantage over the beneficial bacteria that normally are present in the intestinal tract and promotes the severe diarrhea that spreads the bacteria to other people.

The findings are published in the Sept. 23 issue of the journal *Nature*.

"The human body normally has 10 times more microbes than human cells that help protect us against infection from disease-causing bacteria," said Andreas Bäumler, professor of medical microbiology and immunology at the UC Davis School of Medicine and the principal investigator of the study. "We have discovered *Salmonella*'s cunning trick that allows it to quickly take over and outgrow the beneficial microbes in our intestine."

All bacteria must generate energy in order to live and reproduce, either by respiration — which usually requires oxygen — or fermentation. Because essentially no oxygen is available in our intestines, the beneficial bacteria that reside there tend to use fermentation, which is less efficient than respiration for obtaining energy.

When people ingest *Salmonella*, it invades the surface of the intestine. Our immune system responds by producing oxygen radicals to kill the

bacteria. Although some *Salmonella* bacteria are killed by this response, many more benefit: the oxygen radicals create a sulfur compound called tetrathionate, which *Salmonella* are able to use instead of oxygen for respiration.

Interestingly, tetrathionate has been used since 1923 by microbiologists as a way to promote the growth of *Salmonella* in biological samples containing competing microbes. But because tetrathionate was not known to exist in living people, it was assumed prior to this study that this process had little relevance for food poisoning. Up until now, tetrathionate was believed to mainly exist naturally in decaying corpses or in thermal springs.

"Stimulating the host to produce tetrathionate enables *Salmonella* to 'breathe' in the intestine," said Sebastian E. Winter, who is a member of Bäumler's laboratory and lead author of the article. "This gives *Salmonella* a tremendous advantage over the gut bacteria that must grow by fermentation."

By stimulating an inflammatory response in the intestine, *Salmonella* also enhances its transmission to other hosts. The inflammatory response causes the severe diarrhea and vomiting that is the body's attempt to rid itself of the pathogenic bacteria, at the same time enabling *Salmonella*'s spread.

The investigators used a combination of experiments with mouse models and test tubes to study the effects of intestinal inflammation on *Salmonella* and pinpoint the role of tetrathionate respiration. They also used novel techniques from the burgeoning field of metabolomics, which allowed them to measure metabolites in living animals.

Salmonella is frequently in the news as a source of food poisoning outbreaks, usually from eating poorly cooked or unhygienically prepared

eggs or meat. *Salmonella* was the cause of a recall of about half a billion eggs last August and sickened more than 1,500 people. In that case, the ovaries of the hens were contaminated, so the inside of the eggs carried the bacteria and were not safe to eat unless thoroughly cooked. Reptiles such as turtles, lizards and snakes also carry the bacteria on their skin, sometimes causing illness in people who keep them as pets.

Salmonella infection, known as salmonellosis, causes diarrhea, fever, vomiting and abdominal cramps. Although most people recover after several days, it may be fatal, especially in the elderly, infants, and people with an impaired immune system.

For most cases of salmonellosis, antibiotic treatment is counterproductive, as it actually prolongs disease by further inhibiting the growth of beneficial bacteria. Finding that tetrathionate is important in human *Salmonella* infection opens up new avenues for research in finding an effective treatment for salmonellosis.

"Determining how Salmonella is so efficient in outcompeting resident beneficial bacteria is a critical first step in developing new drugs for treating food poisoning," said Bäumler, whose group is now pursuing this avenue of research. "We are hopeful that by targeting sulfur compounds we can stop the bacteria from establishing a foothold in the intestine."

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