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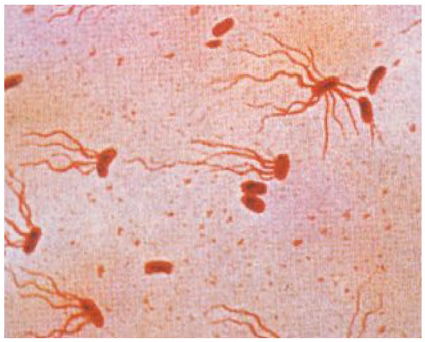
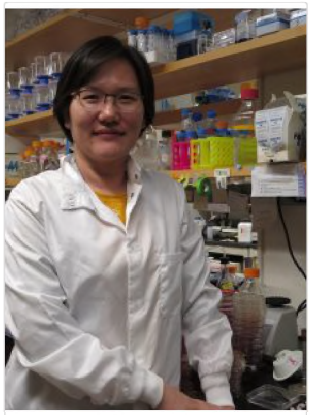


Tricking Typhoid: Researchers Create New Model to Tackle Old Foe

The plague of Athens, presumably caused by typhoid fever, was an epidemic that killed a third of Athens' population during the second year of the Peloponnesian war. The ancient historian Thucydides wrote a detailed account of this event in his book "The history of the Peloponnesian war", making it the first known written description of a typhoid fever outbreak. Since then, other notable cases have made the history books. But even though many years have passed, typhoid fever is still a major public health threat especially for developing countries, where it affects close to 22 million people each year according to the Center for Disease Control (CDC). Dr. Jeongmin Song, assistant professor from the Department of Microbiology & Immunology, studies how the causative bacterium of typhoid fever induces disease using a cell culture set-up as well as a novel mouse model that allows her to recapitulate many of the typhoid fever symptoms in mice.



Dr. Jeongmin Song, assistant professor from the Department of Microbiology & Immunology

The culprit: A bacterial toxin

Typhoid fever is caused by infection with the bacterium *Salmonella* Typhi, and can be acquired by ingesting food or drinks that have been handled by an infected person that is shedding the bacterium in their stool. "Once ingested, the bacteria go inside many cells including epithelial cells in the intestine as well as macrophages," explains Song. Once the bacteria are inside these cells, the bacteria produce typhoid toxin, which is believed to be the cause of some of the symptoms of typhoid fever.

The toxin exits the cells harboring *Salmonella* Typhi and enters the circulatory system. Eventually, the infected person shows signs of a systemic infection characterized by fever, constipation, muscle pain, and loss of appetite Some patients also experience loss of immune cells, a condition known as leukopenia, as well as long-term neurological complications.

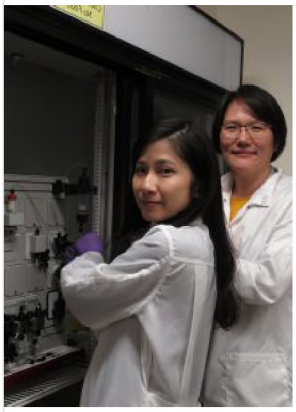
"A major area of research is trying to understand how typhoid toxin gets out of the *Salmonella* Typhi-infected cells and how this causes typhoid fever symptoms," explains Song. Her lab uses a two-fold approach to address these questions: They study intestinal epithelial cells and macrophages in culture to understand how the toxin exits the infected cells; and they use a mouse model to understand what the toxin does once it is in circulation.

A crafty bacterium

Salmonella Typhi has adapted strictly to human hosts, making this pathogen particularly difficult to study in model organisms such as mice. In mice, the bacterium is not able to replicate and therefore the bacterium cannot produce typhoid toxin or cause disease symptoms.

Although mice are immune to the growth of the *Salmonella* Typhi bacterium, they do have the receptor that allows the typhoid toxin to cause disease. "We are able to study the function of the typhoid toxin by injecting typhoid toxin directly into mice," Song explains. She and her

colleagues hypothesized that if the typhoid toxin played a critical role in disease development, they would see typhoid fever symptoms in mice injected with typhoid toxin. Indeed, they determined that mice injected with typhoid toxin showed symptoms characteristic of typhoid fever, including weight loss, loss of immune cells, and motor function deficits. These did not occur in mice that were immunized against the toxin, or in mice that received a mutant version of it.



Dr. Song and her postdoctoral researcher, Dr. Amy Yang

The latest achievement of the Song lab was to determine what type of cells the typhoid toxin targets once it is in circulation. To do this, they labeled the typhoid toxin with a fluorescent dye and then used microscopy to determine its location once they injected it into mice. "Our assumption was that the toxin would be able to bind almost every cell, but we found that that is not the case," says Song. It turns out that the toxin binds only the endothelial cells that line the blood vessels of the arterioles in the brain, which may explain why the toxin is able to cause neurological symptoms in mice. These endothelial cells have the specific glycan receptor to which the typhoid toxin must bind to cause typhoid fever symptoms.

According to Song, "We are still missing key information about the biology of typhoid toxin." Among the next steps for the Song lab is to pharmacologically target the receptor to which typhoid toxin binds to prevent the appearance of symptoms and stop the spread of the disease.

-Luisa Torres, Postdoctoral Researcher in Microbiology & Immunology

2 thoughts on "Tricking Typhoid: Researchers Create New Model to Tackle Old Foe"

1. **Carlos** says:
   October 31, 2017 at 11:10 pm
   Lo leí en inglés y entendí algo. Lo de la guerra del Peloponeso estuvo fantástico como punto de partida. Hubieras regresado a esa guerra a final! Historiadora, también.
   Reply
   1. **lft9** says:
      October 31, 2017 at 11:17 pm
      Gracias por el comentario! Si, tienes razon. Ahi voy aprendiendo.
      Reply

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