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Typhoid Fever Toxin Has a Sweet Tooth

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Salmonella Typhi is the original Typhoid Mary.

Although this insidious bacterium has been around for centuries, very little is actually known about its molecular mechanisms. A new study from researchers at the College of Veterinary Medicine addresses this knowledge gap, and may lead to novel, targeted treatments.

Salmonella Typhi can live either inside or outside host cells. Those living within cells, called intracellular, secrete the typhoid toxin that is responsible for many symptoms of typhoid fever, according to lead author Dr. Yi-An Yang, a postdoctoral researcher in the Song Lab. The research finds that the current vaccine for typhoid fever, called Ty21a, is effective against *Salmonella* Typhi, but not against the typhoid toxin.



Members of the Song Lab. Photo provided.

This new study, published in *Nature Microbiology* on December 4, shows how the toxin exclusively damages selected cells at an organismal level. This toxin has a sweet tooth, specifically seeking cells that express particular sugars because of their binding abilities. When the typhoid toxin finds those cells, it intoxicates them and triggers symptoms such as lethargy, malaise, stupor, decreased white blood cells, and neurological complications.

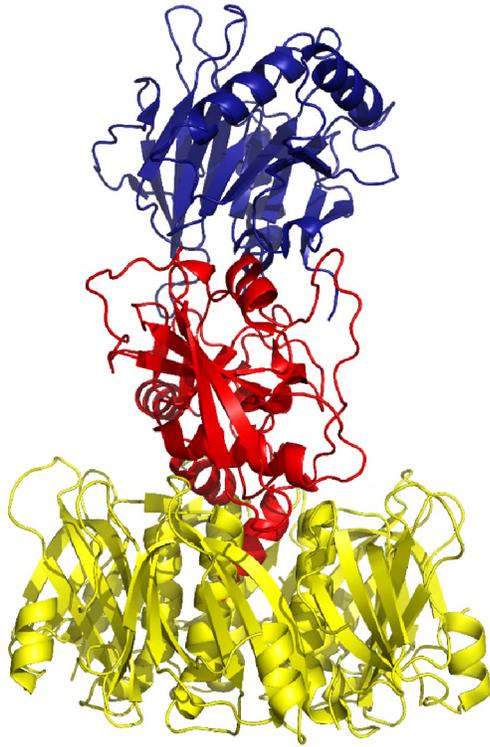
“What’s most exciting is that our results provide insights that may help the development of potential prophylactics and therapeutics to prevent and treat typhoid fever,” said senior author Dr. Jeongmin Song, assistant professor of microbiology and immunology.

Knowing the toxin’s target enables the development of new, non-antibiotic, sugar-based therapeutics, which could help stem the issue of increasing antibiotic resistance.

Typhoid fever is a life-threatening disease often caused by poor sanitation. It afflicts approximately 21.5 million people in the developing world each year, and of the nearly 6,000 cases that appear in the United States, most are acquired internationally, according to the CDC. Sugar-based therapeutics are not limited to typhoid fever, moreover, and may be effective against other diseases in which sugars play crucial roles.

A conjugated vaccine leveraging the toxin combined with Ty21a is likely to be more effective than Ty21a. Researchers found that mice immunized with inactive typhoid toxins presented no symptoms when challenged with a lethal dose of typhoid toxin. Both mice and humans have the sugar-coated cells to which the toxins are attracted, said Yang.

The researchers also found that the toxin, once secreted, doesn’t limit itself to one bodily system in its search for sweets. “Intriguingly, our study shows that the typhoid toxin targets both the immune system and central nervous



Typhoid toxin structure. Photo provided.

system,” said Song. “This represents a new paradigm in the infectious agents’ incursion of the host.” Furthermore, the fact that the two systems must work together to address infectious threats is “a newly established Neuro-Immune Axis paradigm in our body’s responses,” said Song.

The paper is entitled “In vivo tropism of Salmonella Typhi toxin to cells expressing a multiantennal glycan receptor” The DOI is 10.1038/s41564-017-0076-4. The paper can be read in full online.