New study uncovers weakness in C. diff toxin

July 15 2019

A new study, led by researchers from the University of California, Irvine (UCI), uncovers the long-sought-after, three-dimensional structure of a toxin primarily responsible for devastating Clostridium difficile infection (CDI).

Published today in *Nature Structural & Molecular Biology*, the study titled, "Structure of the full-length Clostridium difficile toxin B," sheds light on the weaknesses of TcdB, one of the toxins secreted by the Clostridium difficile (C. diff) bacteria and the main cause of CDI.

"This is the first time we could directly see the 3-D structure of the gigantic TcdB holotoxin at a near atomic resolution," said Rongsheng Jin, Ph.D., a professor in the Department of Physiology & Biophysics at UCI's School of Medicine and the senior author in the study. "Interestingly, this toxin shapes like a question mark when viewed from a certain angle, and it has been a major question for us as we seek ways to fight the toxin and CDI."

Also included in the study, the team demonstrated how three antibodies could neutralize TcdB, revealing intrinsic vulnerabilities of the TcdB toxin that could be exploited to develop new therapeutics and vaccines for the treatment of CDI.

C. diff is an opportunistic pathogen that establishes in the colon when the gut microbiota are disrupted, often seen in severely ill or elderly patients in hospitals or in long-term care facilities. CDI has become the most common cause of antibiotic-associated diarrhea and gastroenteritis-

associated death in developed countries, accounting for half-million cases and 29,000 deaths annually in the US. It is classified as one of the top three "urgent threats" by CDC. The current standard of care for CDI involves treatments using broad spectrum antibiotics that reduce the level of C. diff bacteria, but also kill the good bacteria in the gut and disrupt the normal gut microbiome. This approach often leads to frequent disease recurrence (up to 35%).

Recently, the Food and Drug Administration (FDA) issued a warning about an investigational fecal microbiota for transplantation (FMT) procedure for CDI treatment following the death of patient in a clinical trial. In another action, the FDA approved Bezlotoxumab, a TcdB-neutralizing human monoclonal antibody, as a prevention against recurrent infection.

"There remains a desperate need for more potent and cost-effective therapies for CDI," said Jin. "The good news is, the 3-D structure of TcdB we have identified literally provides a blueprint for the development of next-generation vaccines and therapeutics that have enhanced potency and broad-reactivity across different C. diff strains."

Already the UCI team is working on a novel vaccine based on the new structure. Early studies show promising results, which Jin hopes to publish soon. In the meantime, The Regents of the University of California has filed a patent on their work.

More information: Structure of the full-length Clostridium difficile toxin B, *Nature Structural & Molecular Biology* (2019). DOI: 10.1038/s41594-019-0268-0

Provided by University of California, Irvine