American Journal of Biology and Natural Sciences
https://biojournals.us/index.php/AJBNS
ISSN: 2997-7185

Salmonella Typhi Toxin Promoting

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Received: 2024, 15, Oct
Accepted: 2024, 21, Oct
Published: 2024, 06, Nov

Annotation: Typhoidal Salmonellae and non-typhoidal Salmonellae (NTS) result in typhoid fever and gastroenteritis in humans. Little is understood about the function of the NTS in relation to typhoid disease progression and chronic infection, despite the known role of *Salmonella* typhoid toxin. We discovered that typhoid toxin and its NTS counterpart lead to distinct clinical symptoms. The PltB subunit of every toxin shows distinct glycan-binding preferences that are linked to the glycan expression profiles of host cells at the primary infection or intoxication sites targeted by each bacterium. By examining co-crystal structures of PltB subunits with distinct glycan receptor molecules, we demonstrate that they cause significant variations in glycan-binding affinities and outcomes related to virulence.

Both of these subunits are chemically bonded to each other and join a homopentameric B subunit made up of PltB. It has been recently found that injecting purified typhoid toxin systemically in mice can reproduce several symptoms of typhoid fever. This discovery is very thrilling as it connects typhoid toxin to the development of typhoid fever and offers solid foundations for creating new methods for prevention and

lifesaving treatments. The unique aspect of typhoid toxin is that it is only made by bacteria inside cells and, once it is created, it is released into the vacuole containing *Salmonella*.

Keywords: Salmonella-toxin – mechanism and promoting.

Introduction

Salmonella typhi is a fascinatingly complex bacterium. While there are more than 2000 various strains of *Salmonella*, *Salmonella typhi* is distinct among the non-typhoidal serovars. The symptoms, ways of spreading, and organism that *S. typhi* targets are distinctive because it exclusively impacts humans. Understanding the way bacteria lead to illness is essential for the creation of vaccines. *S. typhi* induces a severe systemic fever known as typhoid fever using a range of intricate molecules, from single proteins to large macromolecules, thanks to sophisticated equipment. The disease often transmits through contaminated food and water supplies and is prevalent in many low- and middle-income nations (1) The disease leads to high levels of illness and mortality globally annually, contributing to financial burdens in both less developed and more developed nations from costs associated with preventing, monitoring, and treating the disease (2,3). Along with *S. typhi*, *S. Paratyphi A* is becoming more prevalent in some regions, causing a rise in associated diseases. The identification of Typhoid toxin (T.T) in typhoidal serovars presents a new angle on the progression of typhoid fever and is proposed as a possible factor in the virulence of *S. typhi*. The typhoid toxin is made exclusively by *S. typhi* within the Salmonella containing vacuole (SCV) in the host cell (4) before being moved to the outside space through a specific method (5,6)

S. typhi, the bacterium that causes typhoid fever, affects approximately 22 million people every year and leads to the deaths of more than 0.2 million individuals annually (7). The global health issue of typhoid fever is greatly influenced by the high prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *S. typhi* strains (8,9). There is a greater prevalence of antibiotic-resistant S. Typhi infection in children, with more than 90% of XDR typhoid cases occurring in individuals younger than 15 years old (10). Prior to the discovery of antibiotics, approximately 25% of people with typhoid fever did not survive .

S. typhi and S. paratyphi serovars both secrete typhoid toxin when infecting, but non-typhoidal serovars typically do not. Unlike CDT, which is present in organisms like *Escherichia coli*, *Haemophilus, and Yersinia*, there are no other exotoxins. Typhoid toxin is made up of a unique A2B5 structure consisting of two distinct A subunits (CdtB and PltA) and a pentameric B subunit comprised of 5 PltB peptides, all found in the chromosome. When typhoid toxin attaches to the target cell surface through the PltB subunit, the CdtB and PltA subunits (referred to as the "A" subunit) enter the cell and CdtB travels through the Golgi apparatus and endoplasmic reticulum before reaching the nucleus. Some research has indicated that typhoid toxin, also known as T.T in the paper, may contribute to the development of typhoid fever. Research has indicated that providing animals with a pure version of typhoid toxin can imitate the symptoms of typhoid fever observed in the initial stage of the disease .However, in order to offer further proof of the impact of toxin in the manifestations of typhoid fever, this research was systematically carried out by incorporating in-vitro, ex-vivo, and in-vivo studies.

It is known that *S paratyphi A* causes the same disease as *S. typhi*, despite not producing Vi. It is clear that *S. typhi* has a range of strategies to cause disease, demonstrating a highly strategic approach to evolution. When developing vaccines, it is important to focus on different aspects of the bacteria to effectively stop the disease.

Many bacteria induce disease symptoms by releasing toxins. The first research on typhoid includes extensive debates on whether the typhoid bacillus produces a toxin, or if the symptoms of the disease were due to components of the cell wall (endotoxin). The second viewpoint held for an extended period. that it was confirmed *S. typhi* releases a toxin outside the cell. The toxin seems to be produced only in specific circumstances, making it difficult to identify until this point. The typhoid toxin, a specific toxin, is a unique combination of toxins from various bacteria and possesses a new structure that has not been recorded before. The fact that the toxin is being seen as a possible focus for a new vaccine is expected.(11)

Our recent research concentrated on utilizing the challenge model to explore a specific virulence factor, with the goal of evaluating the typhoid toxin's potential as a vaccine target in the future. We developed two typhoid strains to infect volunteers: one containing the toxin (wild type) and one without it (toxin knock-out). Our goal was to show the striking similarities between the two strains, with the only difference being the absence of toxin in the knock-out strain. Laboratory experiments were conducted to show that both strains displayed comparable behavior in controlled conditions. With help from the Sanger Institute, we moved forward with sequencing the genome of both strains. We proved that the two strains were identical, except that the wild-type strain had the typhoid toxin which was both present and active. The next step included enlisting a team of dedicated adult volunteers who agreed to be deliberately exposed to *S. typhi* following a comprehensive screening process.

They were randomly chosen to ingest either a wild type or a knock-out strain lacking the typhoid toxin - this involved drinking a solution to neutralize stomach acid followed by consuming a mixture containing around 10,000 *S. typhi* bacteria. We carefully observed the volunteers for at least two weeks, and started treatment when they showed first signs of illness. Typically, about 66% of volunteers became infected with typhoid upon exposure, However, there was an equal frequency of diagnosis between the wild-type and knock-out groups. Overall, the signs and seriousness of the sickness were alike in both groups, along with multiple measures of host immunity. The discovery that individuals with exposure to the toxin knock-out experienced more serious symptoms of the illness, such as prolonged bacteraemia, was a surprise. Our results indicate that the typhoid toxin is not essential for the initiation of acute typhoid in the challenge model. I think there's a high likelihood of having a major impact on diagnosing 'typhoid', even though the specific role is still somewhat unknown. The toxin might alter the host's response to infection and contribute to the development of severe symptoms such as typhoid encephalopathy in typhoid fever.

Yet, the World Health Organization stated in 2018 that there are no vaccines available for infants younger than six months. S. Typhi has the ability to result in serious, possibly lethal diseases, particularly in children who are the most vulnerable. The progression of illness may vary, but usually includes a 1- to 2-week phase of being infected without symptoms, then 2-3 weeks of displaying symptoms, and finally a longer period where some people may unknowingly carry and spread the disease (CDC, 2017). Many factors like typhoid toxin, Vi capsular polysaccharides, and Type III secretion system *Salmonella* Pathogenicity Island (SPI)-1 and SPI-2 effector toxins work together to control the infection process of *S. typhi* (12). Most disease-causing characteristics are located either on the bacteria's surface or inside the host cells infected by *S. typhi*, leading to alterations in host responses primarily at the site of infection and in the infected cells. Unlike other toxins, typhoid toxin is classified as an exotoxin. It impacts host cells in close proximity as well as far from the infected area, assisting the pathogen by altering the quantities and roles of host immune cells (13).

The toxicity was observed only when both PltB and CdtB functions were present, as toxin variants with mutations in glycan-receptor-binding or nuclease functions did not show virulence (14). Therefore, we employed these toxicity measurements in both in vitro and in vivo settings during our investigation of antibody-mediated toxin neutralization. In this study, we demonstrate that antibiotic-resistant *S. typhi* continuously releases typhoid toxin during infection, despite antibiotic treatment, in different infection models and with quantitative techniques. It has been shown that the four toxin-neutralizing epitopes on PltB and CdtB remain consistent across all *S. typhi* clinical isolates, including antibiotic-resistant strains.If this state of intoxication persists, it could result in the death of cells. PltA is an enzyme that transfers a single ADP-ribose molecule and has similarities in both amino acid sequence and structure with pertussis toxin S1 (15). PltB recognizes the specific trisaccharide sequence, N-acetylneuraminic acid (Neu5Ac)-a2-3/a2-6-galactose (Gal)-b1-3/b1-4-N-acetylglucosamine (GlcNAc), as the receptor on host cells for endocytosis, essential for AB toxins to deliver their A subunits to the target site within host cells (13). Likewise, the interaction of PltB with the glycan receptor on the surface of the host cell is crucial in deciding the specificity of bacterial AB toxins towards the host, tissue, and cell types. For example, despite the common occurrence of the trisaccharide in PltB binding, the pentameric structure of PltB allows for precise binding to this sugar pattern in complex N-linked glycoproteins, resulting in strong and multiple interactions. Consistently, typhoid toxin selectively attacks cells containing multiantennary N-linked glycoproteins with numerous Neu5Ac molecules, such as immune cells and arteriolar endothelial cells in the brain (14). Adding an O-acetyl group to the sialic acid Neu5Ac at the end of the glycan receptor appears to influence the typhoid toxin's preference for binding, given that the toxin demonstrates increased affinity for the O-acetylated glycan receptor (Nguyen et al., 2020). The toxin's ability to draw immune cells is anticipated to heavily influence the alteration of innate and adaptive immune responses, which play a role in the suggested roles of this toxin in causing typhoid fever in acute and chronic infections (Song et al., 2013, 2010; Yang et al., 2018a, 2018b).

An interesting aspect of typhoid toxin is that it is produced only in mammalian cells when *S. typhi* is present (15). Once produced, the bacteria release the toxin into the SCV through a newly identified protein secretion system, possibly named type X. The toxin is packaged in vesicle carriers and transported out of the cell. The toxin binds to its specific Neu5Ac-carrying receptors, and is then transported to its intracellular destination through a distinct retrograde transport pathway via receptor-mediated endocytosis (16). Intoxication always requires the toxin to be sent out to the extracellular space because there is no way to move it within the cell from where it is made in the SCV to where it acts according to Spanò et al. (2008). There is limited information on the exocytic pathway that moves the toxin from the SCV to the extracellular space. A mutation in the glycan-binding region of PltB causes a toxin to remain trapped inside the SCV after being released by the bacteria . Toxins are exported through a sorting process, likely assisted by a glycosylated receptor located on the inside of the vacuolar membrane with *S. typhi*.

Conclusion

By merging data from studies conducted in living organisms and in external settings, three key findings were established: 1) the replicated and purged typhoid toxin (holotoxin) causes symptoms resembling typhoid fever in mice. 2) The CdtB subunit of typhoid toxin causes genotoxic impacts on the host DNA, resulting in cell death primarily through Apoptosis. Pre-treatment of the complete toxin with antibodies against CdtB results in decreased DNA breakdown and cell death, suggesting that CdtB is the primary enzymatic component of the toxin.

The neutralizing B cell epitopes on typhoid toxin that stand out preserved in all *S. typhi* clinical strains, alongside the antibody-driven toxin molecular processes bringing to a neutral state. The neutralizing epitopes identified in antibiotic-resistant *S. typhi*, which continues to produce typhoid toxin despite antibiotic treatment, could be used as a foundation for future typhoid treatments. We also anticipate that combining anti-toxin strategies with anti-bacterial strategies (such as anti-LPS, anti-Vi, anti-outer membrane proteins) will result in the highest level of effectiveness. permitting the removal of both the bacteria and the anticipated toxin to be released until full

eradication of bacteria in infected individuals is showed .Our research has revealed how typhoid toxin is transferred from the SCV to the outside of the cell. The export process, tailored for *Salmonella typhi's* biology, has utilized cellular machinery from different secretory and exocytic pathways.

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