BACTERIOLOGY

Toxins in tandem

Analyses of the toxin produced by *Salmonella* Typhi bacteria reveal an unusual assembly of toxin subunits, and show that most symptoms of typhoid fever can be linked to one subunit's DNA-damaging activity. SEE LETTER P.350

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During the complex process of infection, nothing is more fascinating than the interplay between host immunity and pathogen virulence — particularly in asymptomatic carriers, who seem to be in perfect health while normally life-threatening organisms replicate within them. The most infamous such carrier was 'Typhoid Mary', a cook in the United States who infected more than 50 people with typhoid fever by passing on the causative bacterium *Salmonella* Typhi (Fig. 1). Another perplexing feature of these bacteria is the existence of the closely related *Salmonella* Typhimurium, which does not cause life-threatening infections despite having apparently similar virulence properties to *S.* Typhi. A paper by Song *et al.*[1], on page 350 of this issue, places several key pieces in this puzzle.*

MARY EVANS PICTURE LIBRARY

Figure 1 | Typhoid Mary. A classic image of Mary Mallon, an asymptomatic carrier of *Salmonella* Typhi, from public-health posters of the early 1900s. Mary was a cook in New York state who lived a symptom-free life but infected more than 50 people with typhoid fever before health-department detectives traced the epidemics and moved her to involuntary quarantine.

The story centres on one of the few obvious differences between *S.* Typhi and *S.* Typhimurium: the typhoid toxin, which was discovered almost 10 years ago and is specific to *S.* Typhi[2–4]. Typhoid toxin has several features that set it apart from other bacterial toxins. It is known to be assembled from three subunits: CdtB and PltA (proteins with similarities to two disparate classes of bacterial toxins, the cytolethal distending genotoxins (CDT) and the ADP-ribosyl transferases of the pertussis toxin family, respectively), and PltB. But how this dual-activity toxin contributes to the pathogenesis of typhoid fever was, until now, unclear.

Song and colleagues show that, in mice, typhoid toxin alone is sufficient to induce most of the symptoms associated with *S.* Typhi infections, and that these effects are mediated by the DNA-damaging CdtB subunit of the toxin. The authors also show that the toxin is targeted to host cells by interactions with carbohydrate moieties on specific surface glycoproteins. This is a remarkable finding, because previous work had failed to provide a *raison d'être* for CDT toxins in the pathogenesis of other bacteria that carry such proteins. The discovery that the symptoms of typhoid fever depend on CdtB of *S.* Typhi is the first time that the virulence of an organism has been directly linked to the ability of bacteria to induce cellular DNA damage in a host.

The second amazing insight from this study involves the architecture of the typhoid toxin, as revealed by the X-ray crystal structure described by the authors. The structure shows typhoid toxin to be a classic 'AB' type in its general assembly, possessing an active (A) subunit that achieves a biochemical result when a binding (B) subunit interacts with specific cellular receptors. The B subunit of typhoid toxin (PltB) is a homologue of one of the heteropentameric subunits of the pertussis toxin B subunits and, as expected, it pentamerizes with other B subunits. The PltA subunit nestles tightly in the cup that forms at one side of this pentameric disk (see Fig. 3 of the paper[1]).

However, in a striking departure from other known toxin structures, the CdtB subunit of typhoid toxin is not tightly integrated into the main structure, but is 'glued' onto it by a single disulphide bond to the PltA subunit. The authors find that this disulphide bond is crucial for toxin assembly, and that it creates an A_2B_5 organization that has not been seen in any other bacterial toxin. This structure provides two disparate enzymatic activities, only one of which (the DNA-damaging activity) is required to recapitulate most typhoid symptoms.

This unusual tethering of CdtB to PltA could represent a 'missing link' in toxin evolution, in which a factor that confers an advantage to an existing toxin is crudely conjugated in order to associate two cellular activities. Perhaps in several million years, a better-integrated multicomponent toxin will have replaced this one, but for now it is fascinating to obtain this snapshot of evolution in action.

Much remains to be explained. For example, the role of the PltA subunit is not yet accounted for, and although typhoid toxin alone can reproduce many symptoms of typhoid disease, it does not cause the associated fever. However, this work, with its sweeping combination of atomic-resolution reductionism and organismal infection studies, has identified some of the key elements that underlie the unique properties of this pathogen. Our enhanced understanding of the role of the CdtB subunit in *S.* Typhi virulence may open doors to new pharmacological interventions and improved vaccines for an infection for which there are no robust immunization approaches. Typhoid still takes the lives of several hundred thousand people a year[5–7], and the rise of antibiotic-resistant strains of *S.* Typhi could take us back to a situation in which individuals like Typhoid Mary pose a public-health threat. Research to improve our understanding of the disease and to develop treatments is an important undertaking. ■

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