Typhoid toxin increases host survival and promotes asymptomatic infection

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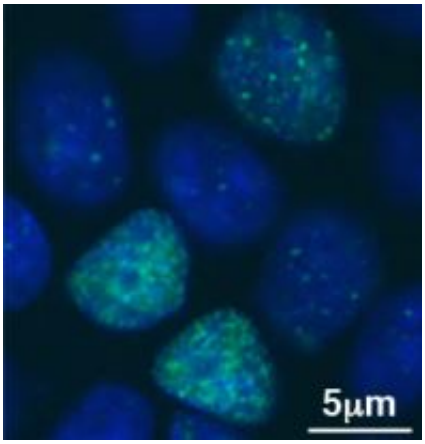

DNA damage following infection with the genotoxin-carrying *Salmonella* strain. Credit: Del Bel Belluz et al.

Genotoxins damage the genetic material in cells and can cause mutations and cancer. Some bacteria code for and produce genotoxins. A study published on April 7th in *PLOS Pathogens* reports the surprising finding that one of them, typhoid toxin, actually increases survival of the infected host and promotes long-term colonization without causing disease in the host. The work, the authors say "poses the semantic and biological question of whether 'toxin' is the appropriate designation".

DNA damage caused by bacterial genotoxins has been linked to cancer, but what, if any, function genotoxins have in the context of a natural infection is not clear. Teresa Frisan, from the Karolinska Institute in

Stockholm, Sweden, and colleagues focused on the typhoid toxin from *Salmonella enterica Typhi* (*S. Typhi*), and specifically looked at chronic asymptomatic infection, which is known to increase the risk for tumors.

S. Typhi infects only humans, making it difficult to study in in vivo mouse models. To get as close as possibly in an animal model, the researchers developed two Salmonella enterica Typhimurium (*S. Typhi*murium) strains, which cause systemic typhoid fever-like infection in immunocompetent mice. In contrast to normal *S. Typhimurium* strains that do not harbor the genotoxin, the two strains were engineered to produce either an active or an inactive typhoid genotoxin.

The researchers infected mice orally with the two bacterial strains and—to their surprise—found that mice infected with the strain carrying the intact typhoid toxin had higher survival rates within the first 10 days post infection. None of the surviving mice from either group fell ill at later stages, but the mice infected with the toxigenic strain were more likely to develop chronic infection without disease signs.

When looking more closely at the early stages of infection, the researchers found that the mice infected with the intact toxin strain mounted a weaker inflammatory immune response in the intestines than mice infected with the strain lacking the functional genotoxin. At other sites of infection throughout the body, however, the situation was consistently different: outside the intestine, the immune response in mice infected with the toxigenic strain was stronger than the response against the control strain.

Since the intestinal microbiota (the community of microorganisms living in the gut) can contribute to the host immune response, the researchers analyzed a total of 35 mouse stool samples collected from uninfected mice and mice infected with the two Salmonella strains. Analyzing bacterial DNA from the stool samples, they found that the presence of

typhoid toxin is associated with a different timing and pattern of the changes in the gut microbiome compared with either no infection or infection with the Salmonella strain that lacks the genotoxin.

The researchers conclude that their data "collectively highlight a novel aspect of typhoid toxin as an immune modulator, which reduces the intestinal inflammatory response and the clearance of the bacteria". Commenting on the potential link between genotoxins and cancer, they say "in our experimental conditions, chronic infection was not associated with induction of dysplasia or pre-carcinogenic lesions within the study period".

More information: Del Bel Belluz L, Guidi R, Pateras IS, Levi L, Mihaljevic B, Rouf SF, et al. (2016) The Typhoid Toxin Promotes Host Survival and the Establishment of a Persistent Asymptomatic Infection. *PLoS Pathog* 12(4): e1005528. DOI: 10.1371/journal.ppat.1005528