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Development of a novel chimeric toxin vaccine against *Clostridium difficile* infection

Hanping Feng
University of Maryland, USA

The global emergence of *Clostridium difficile* infection (CDI) has contributed to the recent surge in severe antibiotic-associated diarrhea and colonic inflammation. *C. difficile* produces two homologous glucosylating exotoxins, TcdA and TcdB, both of which are pathogenic and require neutralization to prevent disease occurrence. However, because of their large size and complex multifunctional domain structures, it has been a challenge to produce native recombinant toxins that may serve as vaccine candidates. Here, we describe a novel chimeric toxin vaccine that retains major neutralizing epitopes from both toxins and confers complete protection against primary and recurrent CDI in mice. Using a nonpathogenic *Bacillus megaterium* expression system, we generated glucosyltransferase-deficient holotoxins and demonstrated their loss of toxicity. The atoxic holotoxins induced potent antitoxin neutralizing antibodies showing little cross-immunogenicity or protection between TcdA and TcdB. To facilitate simultaneous protection against both toxins, we generated an active clostridial toxin chimera by switching the receptor binding domain of TcdB with that of TcdA. The toxin chimera was fully cytotoxic and showed potent proinflammatory activities. This toxicity was essentially abolished in a glucosyltransferase-deficient toxin chimera, cTxAB. Parenteral immunization of mice or hamsters with cTxAB induced rapid and potent neutralizing antibodies against both toxins. Complete and long-lasting disease protection was conferred by cTxAB vaccinations against both laboratory and hypervirulent *C. difficile* strains. Finally, prophylactic cTxAB vaccination prevented spore-induced disease relapse, which constitutes one of the most significant clinical issues in CDI. Thus, the rational design of recombinant chimeric toxins provides a novel approach for protecting individuals at high risk of developing CDI.

Biography

Hanping Feng is an Immunologist with strength in the areas of Cell Biology and infectious diseases. He is an Associate Professor in the Department of Microbial Pathogenesis and Department of Microbiology and Immunology at the University of Maryland Baltimore. He is holding multiple NIH awards and leading a research team to study host immune response to *Clostridium difficile* infection and to design immune-based interventions against these diseases.

HFeng@umaryland.edu