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A novel chimeric toxin vaccine against Clostridium difficile infection

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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 structure, 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 non-pathogenic Bacillus megaterium expression system, we generated glucosyltransferase-deficient holotoxins and demonstrated their loss of toxicity. The atoxic holotoxins induced potent anti-toxin 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 TcdA. The toxin chimera is 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 has obtained his Ph.D at the Department of Microbiology and Immunology at the University of Arizona in 2002 and had his postdoctoral training at Harvard Medical School. In 2004, Feng was recruited to Tufts University Cummings School Veterinary Medicine as a Research Assistant Professor and was promoted to Associate Professor in 2010. In the end of 2011, Dr. Feng's lab was moved to the Department of Microbial Pathogenesis at the University of Maryland Dental School. His current research focus is on the pathogenesis of Clostridium difficile infection and the development of immune interventions against the disease. He has published more than 30 research papers in past 10 years.

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