**Underlying mechanism of antimicrobial activity of chitosan microparticles and implications for the treatment of infectious diseases**

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The emergence of antibiotic resistant microorganisms is a great public health concern and has triggered an urgent need to develop alternative antibiotics. Chitosan microparticles (CM), derived from chitosan, have been shown to reduce E. coli O157:H7 shedding in a cattle model, indicating potential use as an alternative antimicrobial agent. However, the underlying mechanism of CM on reducing the shedding of this pathogen remains unclear. To understand the mode of action, we studied molecular mechanisms of antimicrobial activity of CM using in vitro and in vivo methods. We report that CM are an effective bactericidal agent with capability to disrupt cell membranes. Binding assays and genetic studies with an ompA mutant strain demonstrated that outer membrane protein OmpA of E. coli O157:H7 is critical for CM binding, and this binding activity is coupled with a bactericidal effect of CM. This activity was also demonstrated in an animal model using cows with uterine diseases. CM treatment effectively reduced shedding of intrauterine pathogenic E. coli (IUPEC) in the uterus compared to antibiotic treatment. Since Shiga-toxins encoded in the genome of bacteriophage is overexpressed during antibiotic treatment, antibiotic therapy is generally not recommended because of high risk of hemolytic uremic syndrome. However, CM treatment did not induce bacteriophage or Shiga-toxins in E. coli O157:H7; suggesting that CM can be a potential candidate to treat infections caused by this pathogen. This work establishes an underlying mechanism whereby CM exert antimicrobial activity in vitro and in vivo, providing significant insight for the treatment of diseases caused by a broad spectrum of pathogens including antibiotic resistant microorganisms.