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Secreting an enterotoxin

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Summary

Understanding the secretion of an enterotoxin by enterotoxigenic *Escherichia coli* strains paves the way to the development of new drugs

Significance and context

To date, four classes of enterovirulent *Escherichia coli* strains have been described, all of which cause gastroenteritis in humans. Among these are the enterotoxigenic *E. coli* (ETEC) strains that have been associated with diarrheal illness in all age groups from diverse locations. Infection with ETEC causes a cholera-like diarrhea in infants in less-developed countries and in visitors there from industrialized countries. (A better known name of the disease is traveler's diarrhea.) Every year, approximately 380,000 children less than 5 years old die from illness caused by infection with ETEC. It has been demonstrated that ETEC strains produce and secrete one or both types of enterotoxins, namely heat-stable enterotoxin (ST) and heat-labile enterotoxin (LT); the ST form survives boiling for 30 minutes, in contrast to the LT form. A better understanding of the toxin-secretion systems could improve prevention and treatment of ETEC-induced illness.

Although detailed studies on the action of LT have been performed, how it is secreted by ETEC remains largely unknown. LT and the cholera toxin (CT), produced by *Vibrio cholerae*, are structurally and biologically related. *V. cholerae* secretes both plasmid-encoded LT and CT, a process which takes place in two steps. First, two subunits are translocated towards the periplasm, where they undergo folding and assembly. Second, the holotoxin is transported across the outer membrane via a type-II protein secretion pathway. Upon introduction of the plasmids into the nonpathogenic *E. coli* K-12 strain, however, LT and CT accumulate mainly in the periplasm, in contrast to ETEC LT-secreting isolates from humans. Tauschek *et al*. characterized a type-II protein secretion pathway present in ETEC but absent from *E. coli* K-12, and demonstrated that this pathway is required for the secretion of the LT.

Key results

Previously, a type-II secretion system was identified in a rabbit-specific enteropathogenic *E. coli* strain. This sequence was used as a template to design primers that were used to isolate a similar genetic locus in the human ETEC strain H10407. A locus of 11,765 bp was isolated that contained 13 open

reading frames. Surprisingly, only the flanking regions of this locus were present in *E. coli* K-12. The open reading frames were annotated as *pppA*, *yghG*, and *gspC-M*. The predicted PppA protein was significantly similar to a prepilin peptidase required for CT secretion by *V. cholerae*; *yghG* encodes a putative outer membrane lipoprotein; and GspC-M proteins were most similar to type-II secreted proteins from *V. cholerae*. The *gspD* and *gspK* orthologs were present in a variety of ETEC strains, independent of whether they produced LT, ST, or both.

To demonstrate that the type-II protein secretion pathway is required for LT secretion, a kanamycin-resistance cassette was integrated into the *gspD* gene of ETEC H10407, creating mutant MT13. The analysis showed that MT13 was able to synthesize the LT, which accumulated in the periplasm. In contrast, the parental strain secreted LT into the medium. The MT13 LT was shown to be biologically active, as Y1 adrenal cells changed their shape from an elongated spindle-like morphology into a more rounded shape upon treatment with either MT13 or H10407 LT.

Links

More detailed information about enterovirulent *E. coli* strains and useful links are presented at the Bacteriology at University of Wisconsin-Madison, Bacteriology 330 Pathogenic *E. coli* website.

Reporter's comments

Tauschek *et al*. identified a type-II protein secretion system present in a variety of enterotoxigenic *E. coli* strains but not in the nonpathogenic K-12 strain. This study adds to our understanding of how *E. coli* cholera-like toxins are secreted. Future work should focus on the detailed molecular analysis of this secretion system as well as on how the various genes encoding this type-II secretion system are regulated. A proteomics approach might uncover additional proteins that are required for virulence and are also transported across the outer membrane via the type-II secretion system described by Tauschek *et al*. This detailed study of the mode of action of a specific type-II protein secretion system may allow the development of new drugs that specifically inhibit the secretion of ETEC toxins and/or other proteins, and that may be used as prevention of or therapeutics against ETEC-induced disease

Table of links

Proceedings of the National Academy of Sciences of the United States of America

Pathogenic *E. coli*

References

1. Tauschek M, Gorrell RJ, Strugnell RA, Robins-Browne RM: Identification of a protein secretory pathway for the secretion of heat-labile enterotoxin by an enterotoxigenic strain of *Escherichia coli*. Proc Natl Acad Sci USA. 2002, 99: 7066-7071.