Table of Contents
C&EN Classifieds
News of the Week
Cover Story
Editor's Page
Business
Government & Policy
Science/Technology
Concentrates
- Business
- Government & Policy
- Science/Technology

Education
ACS News
Calendars
Books
Digital Briefs
ACS Comments
Career & Employment
Special Reports
Letters
Newscripts
Nanotechnology
What's That Stuff?
Pharmaceutical Century

Hot Articles
Safety Letters
Chemcyclopedia

Back Issues
2001 Go!

How to Subscribe
Subscription Changes
About C&EN
Copyright Permission
E-mail webmaster

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[Previous Story] [Next Story]

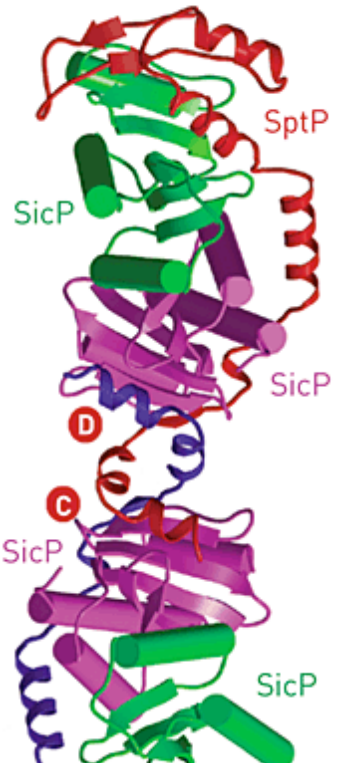
THREADING A NARROW NEEDLE

Bacterial chaperones keep proteins unfolded for injection into cells

CELIA HENRY

A high-resolution crystal structure obtained by Jorge E. Galán, a microbiologist at Yale School of Medicine, and former postdoc C. Erec Stebbins, now at Rockefeller University, sheds some light on the type III secretion system used by many pathogenic bacteria to inject effector proteins into host eukaryotic cells. The structure could help in identifying or designing compounds to interfere with the secretion system.

This type III delivery system consists of a needlelike appendage on the surface of the bacterium. The bacterial proteins have to travel through this needle to reach the cell. However, the opening of the needle is only about 30 Å--too small for a folded protein to fit through. "The $64,000 question has always been, 'How do the proteins travel through these particular structures?' " Galán says.



Each protein is associated with a chaperone protein inside the bacterial cell. The chaperones are vital to the operation of the secretion system, but what hasn't been clear until now is what role they play.

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UNFOLDED Chaperones hold effector proteins in an unfolded conformation. The crystal unit consists of a homodimer containing four chaperones (green and magenta) and two effector proteins (red and blue). The important regions of contact between the chaperones and effectors are labeled A–D. *NATURE*, © 2001

Galán and Stebbins obtained a crystal structure at 1.9-Å resolution of a *Salmonella* chaperone known as SicP together with its associated protein, known as SptP. The structure reveals that the chaperone molecules hold the effector protein in an unfolded conformation [*Nature,* **414**, 77 (2001)]. "That immediately suggests that proteins travel through the syringe in an unfolded conformation, which is consistent with the idea that if they were folded in a three-dimensional structure, the molecule would be too big to fit through the hole," Galán says.

However, the protein is not completely unfolded. It still maintains secondary structure such as a-helixes and b-sheets. "One of the big questions in the field was how are these structures being recognized," Galán says. "Presumably, the key here is that some secondary structural features are maintained by the chaperone and somehow the syringe sees them," Galán speculates.

"Previous research suggested these chaperones may act as secretion pilots or bodyguards protecting the effector from making improper or premature interactions," says Craig L. Smith, a microbiology postdoc at Washington University School of Medicine, St. Louis, and a coauthor of an accompanying commentary. "It appears from the structure that the chaperone keeps the cognate effector protein in a partially unfolded state ready for secretion. These chaperones may be acting both as secretion pilot and bodyguards."

Two other reports--one from the group of Natalie C. J. Strynadka at the University of British Columbia and the other from Partho Ghosh at the University of California, San Diego--detail the crystal structures of other type III secretion chaperones, albeit without their associated effector proteins [*Nat. Struct. Biol.,* advance online publication, published Oct. 29, http://www.nature.com/nsb; *Nat. Struct. Biol.,* **8,** 974 (2001)]. The structures of those chaperones are similar to the one solved by Galán and Stebbins, leading Galán to believe that their findings will be universal.

[Previous Story] [Next Story]

Top