Exotoxins

Author: Lundmark, Cathy

Source: BioScience, 57(4) : 384

Published By: American Institute of Biological Sciences

URL: https://doi.org/10.1641/B570415

Exotoxins

ESTUARINE WHODUNIT

Remember the fish kills that precipitated "*Pfiesteria* hysteria" in the media 10 years ago? A break in the mystery, and an end to the ongoing controversy over what caused so many fish deaths in eastern US estuaries and threatened the health of numerous watermen and marine lab personnel, may be at hand. Scientists in Charleston, South Carolina, led by NOAA's Peter Moeller at the Hollings Marine Laboratory, have identified a highly unstable toxin produced by the toxic form of *Pfiesteria piscicida*. Their work is published in the 15 February issue of *Environmental Science and Technology*.

The dinoflagellate at the center of the turmoil, *P. piscicida*, has been reported to have a complex life cycle consisting of a number of different forms, making it difficult to track and fueling the controversy over its toxicity. Some strains are toxic, but only under certain conditions and for a short time, presenting a serious challenge to researchers trying to study their toxicity and its mode of action. To complicate matters, the dinoflagellate itself disappears rather abruptly from the site of a fish kill, becoming a dormant cyst or leaving the water column by attaching to dying and dead fish to consume their tissues.

What ultimately led Moeller and colleagues to identify the toxins produced by *Pfiesteria*—there are more than one—was the presence of a heavy metal, copper or iron, as a core element. Their instability in purified form and their sensitivity to white light also made the toxins particularly tricky to characterize. It took chemists and toxicologists working in darkroom-like conditions, using multiple sophisticated methods, to work out the details of the deadly molecules. Nuclear magnetic resonance showed the toxins were made up of simple hydrocarbon chains linked to another element, which mass spectrometry revealed to be sulfur. Inductively coupled plasma mass spectrometry detected the high concentrations of copper and iron in the toxic fractions. Another type of mass spectrometry confirmed that the molecules are made up of hydrocarbons and that they rapidly decompose. X-ray absorption spectroscopy confirmed the presence of copper (the iron-based toxins require further study) and suggested the copper binds with either the sulfur or another copper atom.

Another technique, using electron paramagnetic resonance spectroscopy and spin trapping, showed that as toxins break down in the presence of light, their metal core can generate free radicals, which are extremely destructive to living tissues and may be the major source of toxicity. It remains to be seen whether one of these newly identified toxins is responsible for the havoc wreaked by *Pfiesteria*. The next step will be to catch one in the act, at the scene of a fish kill, to see if *Pfiesteria* toxin and its free radical spinoffs are present and accountable.

BINDING AND ENTERING

Gram-negative pathogenic bacteria, such as *Pseudomonas aeruginosa*, have evolved a variety of mechanisms to deliver exotoxins directly into host cells. The most complex of these, the type III secretion system, comprises about 20 proteins that are homologous to the flagellar biosynthesis apparatus of bacteria.

Researchers from the University of California–San Francisco, led by senior author Joanne Engel, have identified a host protein, a ubiquitin ligase called Cbl-b, that helps protect mice from infection with *P. aeruginosa*. It works by targeting a type III secretion system component, an exotoxin and virulence factor called ExoT, for degradation once it enters the host cell. The study appears in the February issue of the *Journal of Clinical Investigation*.

An opportunistic pathogen commonly acquired in hospitals, *P. aeruginosa* attacks patients with epithelial injury or compromised immunity and can cause acute pneumonia or systemic infection. ExoT, which is thought to play an important role in *P. aeruginosa* pathogenesis, disrupts the cytoskeleton of host cells and inhibits a number of functions, including wound healing and signaling required for an immune response.

In experiments with mice, researchers were able to elucidate an early stage of defense against opportunistic infection. They showed that soon after infection with *P. aeruginosa*, the exotoxin injected into host cells is blocked by ubiquitin ligase Cbl-b, which targets ExoT for demolition by attaching ubiquitin residues to the appropriate site. Knowing the details of this innate defense response may lead to better strategies for dealing with these infections.

Cathy Lundmark (e-mail: clundmark@aibs.org).

doi:10.1641/B570415
Include this information when citing this material.