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# Anthrax paralyzes immune cells with lethal toxin

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University of Florida researchers have revealed how the inhaled form of anthrax paralyzes the body's defenses and prevents immune cells from reaching the site of infection.

Anthrax killed five people in 2001 when letters containing the bacteria's spores were sent through the mail. The UF findings, published last week in the EMBO Journal, may lead to quicker diagnoses for anthrax victims.

The disease causes flu-like symptoms that can take weeks to develop, according to the Centers for Disease Control and Prevention. But once the first symptom appears, the disease progresses rapidly and patients often die from shock before they realize they have more than a common cold. The current method of detecting anthrax relies on lab cultures that can take days to complete.

"We're looking for approaches to detect anthrax earlier in the blood," said Russell During, a postdoctoral fellow at UF's College of Medicine. "We're trying to develop a test that would allow detection within two or three hours of the bugs entering the blood and secreting toxins."

Once inhaled, anthrax releases a lethal toxin that immobilizes the white blood cells that normally seek and destroy invading bacteria. Just traces of the toxin can slow movement of these cells, called neutrophils, by 50 percent, UF researchers discovered.

"Neutrophils have to get to the infection to kill anything. If you paralyze

them so they don't move, they can't protect you," said Dr. Fred Southwick, division chief of infectious diseases at the UF College of Medicine and the study's lead author.

But exactly how the anthrax toxin wards off neutrophils has puzzled scientists for years. Immune cells rely on rod-shaped filaments called actin to propel them toward an infection. In a previous study, Southwick found that the toxin prevents actin assembly, leaving neutrophils stuck in the mud.

"Actin is important because it's the motor that causes neutrophils to move," said Southwick. "So it's like cutting the gas to the motor."

Anthrax literally cuts the gas line. The toxin works like a pair of scissors, snipping off the ends of a key protein and preventing the transmission of messages within the cell. As a result, immune cells never receive the green light to assemble the actin motor, Southwick's findings demonstrate.

"Together, these studies provide important clues about how anthrax escapes the immune system during infection," said Nick Duesbery, deputy director for research operations and senior scientific investigator at the Van Andel Institute in Grand Rapids, Mich.

In 1998, Duesbery discovered that the toxin interrupts the transmission of signals within cells. But Southwick's study is the first to explain how anthrax can short-circuit a cell signal to block neutrophil movement, a realization that has eluded scientists for years. The finding almost escaped Southwick's research team as well, which was looking for proteins that interacted directly with the toxin.

"I would say it's the scientific equivalent of finding a needle in a haystack," Southwick said.

The team compared before and after snapshots of neutrophils exposed to a purified form of the toxin, as well as images showing how protein expression changed in cells. After scrutinizing the images for hours, During finally identified one protein that seemed to disappear upon exposure to anthrax.

The protein turned out to be responsible for gathering the components of actin and shuttling them to the center of the cell, where they are assembled into filaments.

“We’ve discovered that through this pathway, lethal toxin blocks the function of a protein that regulates how actin assembles,” said Southwick, who believes his findings may also explain how anthrax paralyzes other types of cells, like the platelets that normally help blood clot.

“We know that patients with anthrax bleed,” Southwick said, adding that victims of inhalational anthrax often suffer hemorrhages in their lungs and lymph nodes. “No one understands why, and it could very well be due to paralysis of platelets.”

During and Southwick are currently looking for additional proteins targeted by anthrax. They hope to develop a diagnostic blood test that detects the bacterium by checking for telltale changes in protein expression.

Southwick’s team used an unusual approach to tease out the anthrax toxin’s effects on cell migration: They allowed the immune cells to be hijacked by another bacterium, Listeria monocytogenes. Listeria is often used as a tool to study actin because it commandeers human cells and induces them to form the filaments, which the bacteria use to navigate around the body.

“We used one bacterium to weed out another. I’m not aware of anyone ever doing that,” Southwick said. “In an individual cell, you can’t figure out where the actin is assembling and what’s controlling it. But Listeria seems to use the same pathways that a cell uses to crawl. So anything that blocks Listeria we predict would also block neutrophils from crawling. And that’s what we found.”

Source: University of Florida