The Best Offense Against Bacteria is a Good Defense

Research shows small proteins called defensins neutralize toxins released by pathogens

By: Emily Caldwell

Published on January 07, 2015

COLUMBUS, Ohio – A small protein active in the human immune response can disable bacterial toxins by exploiting a property that makes the toxins effective – but also turns out to be a weakness.

These toxins, which are released by bacteria, have malleable surfaces that allow them to move through porous areas of host cells to pave the way for bacteria to stay alive. But that same malleability makes the toxins vulnerable to these immune system proteins, which bind to the toxins and render them useless.

The small proteins are called defensins, and are peptides made up of about 30 amino

acids. Scientists have known defensins can neutralize bacterial toxins for about a decade, but until now didn't know how.

Though the researchers used a single defensin for most of their experiments, their work with a handful of others suggests that all defensins are similar enough to share this capability. This makes defensins a potentially promising model for the development of drugs that could mimic their activity and reduce pathogens' infectious power.


Dmitri Kudryashov

" An important part of our findings is that the defensin offers universal protection. Not every single toxin will be affected, but many toxins will, said Dmitri Kudryashov, assistant professor of chemistry and biochemistry at The Ohio State University and senior author of the study.

" They are less potent than an acquired antibody response, but that response takes time. So when the body meets a pathogen for the first time, defensins provide a less efficient but universal defense. This is what gives them their strength."

The research is published in a recent issue of the journal Immunity.

Defensins are part of the innate immune system – the first line of defense when a pathogen invades the body. Two types of cells that function as shields against pathogens secrete defensins after they've recognized an infectious organism is in their midst.

On the other side of the interaction, invading infectious bacteria produce toxins – which are also proteins – that can travel to distant locations and perform functions that make the host conditions more conducive to bacterial survival. Several of the toxins' techniques involve destabilizing host cells so they are unable to participate in attempts to fight or kill the invading bacteria.

In a previous paper, Kudryashov and colleagues described how toxins' lack of structural rigidity is a secret to their success – they can unfold themselves to cross a host cell membrane and then refold into their toxic structure on the other side, within the cell.

" This is a very sophisticated and smart way for bacterial toxins to function," Kudryashov said. " Many different toxins are released distantly, and that's why it's so important to neutralize them."


Elena Kudryashova

That same lack of rigidity, however, is what makes the toxins susceptible to the neutralizing effects of defensins, said lead author Elena Kudryashova, a research scientist in chemistry and biochemistry at Ohio State.

Defensins can exploit toxins' ability to change their structure by attaching to specific locations on these proteins, triggering misfolding to occur at an inopportune time.

" Defensins become part of the toxin that is not properly folded. They integrate into the toxin in such a way that means it basically cannot accomplish its functions," Kudryashova said.

To confirm the mechanism, the researchers conducted numerous test-tube experiments using a single type of a known human defensin against toxins that are associated with a variety of infectious bacteria, and then extended the work with tests using additional defensins as well. The scientists also added salts and other substances to the experimental solution, reproducing physiological conditions to show defensins would be active under those circumstances.

The research confirmed this universal ability for defensins to recognize and disable bacterial toxins, and also showed that defensins appear to restrict their neutralizing behavior to toxins and not other proteins that must function properly to maintain human health. These features make them attractive drug models that could be part o an arsenal of agents likely to be needed to combat antibiotic-resistant bacteria.

The research team is now testing defensins' effectiveness against viral proteins.

This work was supported by an Ohio State start-up fund, the National Institutes of Health and the National Science Foundation.

Co-authors include Royston Quintyn and Vicki Wysocki of chemistry and biochemistry; and Stephanie Seveau of microbiology and microbial infection and immunity, all at Ohio State; and Wuyuan Lu of the University of Maryland School of Medicine.

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