UC SANTA BARBARA

THE Current

November 28, 2018
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Breaching the Walls

In a development that could lead to better drug delivery systems and modern antibiotics, UC Santa Barbara researchers have uncovered a novel mechanism by which strains of bacteria target and destroy their rivals in their never-ending quest for niche domination.

“What we’re studying is how bacteria engage in warfare — try to kill each other to compete for resources,” said Zachary Ruhe, a postdoctoral scholar in the lab of UC Santa Barbara biology professor David Low. “And they do this in a variety of different ways.”

Indeed, the strategies that bacteria employ to dominate their niche are diverse, from approaches that overrun the competition through sheer volume and adaptations that make them most suitable to their niche, to tactics that selectively impair their rivals’ essential functions and the deployment of toxins to weaken or kill them.

In their paper “Programmed Secretion Arrest and Receptor-Triggered Toxin Export during Antibacterial Contact-Dependent Growth Inhibition,” published in the journal CELL, lead author Ruhe and colleagues describe a surprisingly sophisticated mechanism that a particular strain of *E. coli*, EC93, employs to inhibit rival *E. coli* bacteria. Of particular interest is its procedure of targeting and delivering the toxin to only specific cells, a method that could be a solution to the problem of antibiotic resistance.

“It’s a two-step process,” Ruhe said of the contact-dependent inhibition (CDI) system. First, he explained, the bacterium picks a target. In this case the target is typically in the same species — but not closely related enough — since different strains of the same species of bacteria are usually each other’s biggest competitors for a given niche.

To find this distant relative, EC93 goes fishing.

“First what it does is present a sensor domain, which is basically a long filament with a little adhesion domain at the tip,” Ruhe explained. When this sensor filament, representing approximately half of a single large protein, finds its target molecule on the surface of a nearby bacteria, it binds to it. Then EC93 mounts the second stage of its attack.

“Secretion resumes and the toxin delivery device then gets exported,” Ruhe said. In a move the scientists believe evolved to overcome the target gram-negative bacteria’s extra outer layer of defense — one mechanism of antibiotic resistance — a translocator channel (“translocon”) folds into the outer cell wall at just the right time. This allows the attacking bacteria to breach its distant cousin’s outer defenses, after which the victim’s own processes do the work of taking up the toxin through its energized inner membrane.

“So thermodynamically, this system can get across what we call non-energized barriers,” Ruhe explained. The mechanism, in principle, can be used to cross any cell membrane — a major challenge in drug delivery.

Of particular interest to the scientists is the timing of this translocon protein folding, a targeted process that occurs only when the initial “fishing rod” filament has made sufficient contact with the target cell’s surface. Too soon and the energy for the process, which comes solely from the protein folding, dissipates, and the attack is unsuccessful. Too late, and contact with the target may be lost.

“It’s pretty incredible, this long protein that does it all,” said Kiho Song, a graduate student in UCSB biology professor Christopher Hayes’ lab, whose job it was to determine the roles each part of the CDI system plays in this novel process. “It’s very sophisticated with multiple controls along the way.” For instance, he said, if the CDI does not halt secretion of the filament at a specific site, the filament eventually falls off. So for the system to work properly it has to pause. The researchers are interested in, among other things, the molecular processes that arrest secretion and

override that arrest.

This work, they say, has powerful implications for the ongoing effort to find better, “smarter” antibiotic therapies. Because this mechanism is targeted, it could be programmed to selectively attack certain pathogens, whereas the current method is to destroy an entire microbial community with conventional broad-spectrum antibiotics.

“We sort of carpet bomb when we use antibiotics,” Ruhe explained. “We get rid of the bad actors, but we also get everyone else that are actually doing some good for us, what we call ‘commensal bacteria.’” Prolonged use of broad-spectrum antibiotics has resulted in pathogenic bacteria strains developing resistance and becoming difficult-to-treat superbugs. We could instead be helping our good-guy bacteria get an edge on their competition by taking out only the bad guys, Ruhe said, and this approach could provide another option to the evolutionary arms race between humans and their bacterial pathogens. Specific toxins might also be deployed for even more precise targeting.

Additionally, this method may assist in unraveling the physical mysteries of microbial communities in places such as the gut. The CDI mechanism could be tweaked for use as a sensor for cell-cell contact, Ruhe said.

“We can create a ‘microbiome roadmap,’” he said, which would lead to a basic understanding of how the many and varied bacterial communities in our gut assemble and organize themselves, and therefore interact with one another in ways that may shed light on how they affect our health.

Research on this project was conducted also by Josephine Nguyen of UCSB, and Poorna Subramanian, Taylor Stevens and Grant Jensen of the California Institute of Technology.

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