Learning the language of bacteria

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Bacteria are among the simplest organisms in nature, but many of them can still talk to each other, using a chemical "language" that is critical to the process of infection. Sending and receiving chemical signals allows bacteria to mind their own business when they are scarce and vulnerable, and then mount an attack after they become numerous enough to overwhelm the host's immune system.

This system, called "quorum sensing," is an interesting example of sophistication among microbes, says Helen Blackwell, an associate professor of chemistry at the University of Wisconsin-Madison. In practical terms, she adds, quorum sensing may provide an alternative therapeutic target as bacteria continue to evolve resistance to antibiotics.

Theoretically, blocking quorum sensing would prevent the bacteria from turning pathogenic and producing the toxins that are an immediate cause of disease in bacterial infections.

Bacteria use simple chemical signals to control quorum sensing, and Blackwell is interested in how these compounds work and in developing new ways to intercept them. In a study just published online in the journal *ChemBioChem*, Blackwell and colleagues Andrew Palmer, Evan Streng and Kelsea Jewell showed that several species of bacteria can respond to identical signals, suggesting that one drug could battle quorum sensing in several types of bacteria.

Many bacteria use a class of molecules called lactones for quorum sensing, and Blackwell's lab has synthesized many non-native lactones, and then tested them in two species of bacteria that use identical native lactone signals. Overall, the organisms responded similarly to the same synthetic molecules, despite the dramatic differences between the species.

These results suggest that the same basic chemical sensing mechanism could be common among microbes, Blackwell says. "That tells us that we can use these classes of chemicals to study — and perhaps eventually fight — a much broader range of bacteria."

Finding a broad-spectrum activity for the synthetic lactones is good news, Blackwell adds. "Bacteria come in countless varieties, and the ability to target multiple organisms with one compound could streamline the search for drugs. At the same time, we also have found differences in signal selectivity that may allow us to target some bacteria while ignoring others."

That could provide the best of both worlds, Blackwell says. One drug might halt multiple infections, but related drugs might affect only one microbe in a mixture. "The data indicate that it should be possible to design and use compounds that are either selective or broad-spectrum."

The non-native signaling compounds tested in Blackwell's study were first uncovered in Vibrio fischeri, the bacterium that produces light in the "flashlight squid," which lives in the Pacific Ocean. The flashlight squid and its glowing bacteria have a symbiotic relationship that benefits both parties and have been intensely studied by Ned Ruby and Margaret McFall-Ngai at UW-Madison. But quorum sensing is also active in bacteria that cause disease in animals and plants, Blackwell says.

The need for new ways to control bacteria reflects the rapid evolution and spread of bacterial resistance to the most powerful antibiotics. Antibiotics are no longer a high research priority at most pharmaceutical companies,

Blackwell says. "There is a crisis in antibiotic development, and there is a tremendous need to develop new ways to block bacterial infection. Academics can lead the way by identifying such targets"

Quorum sensing has attracted considerable interest as a way to keep bacteria from "behaving badly," Blackwell says. Because a drug that blocks the quorum signal would not kill bacteria but simply prevent them from releasing toxins and causing disease, "we anticipate that the bacteria are not going to develop resistance as quickly, if at all."

Blocking the quorum sensing system would be equivalent to using white noise to interfere with spoken communication, Blackwell adds. "Bacteria are always looking out for themselves, and they are looking for food and a safe place to live. If they try do this as individual cells, the host will fight them off, but as a group, bacteria can potentially overwhelm their host. If we can figure out how to stop them from 'counting themselves' via quorum sensing, we could block such group behavior, and that is what we are after."

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