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Quiet Bacteria and Antibiotic Resistance

Bacteria devoted to growth instead of "quorum sensing" communication could beat antibiotic resistance

By Melinda Wenner

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Despite the rising menace of bacteria—at roughly 19,000 a year, more Americans die from drug-resistant Staphylococcus aureus infections than from HIV/AIDS—the microorganisms do deserve some credit for their cleverness. Antibiotic-resistant strains reared their heads 60 years ago, and ever since scientists have been struggling to develop second-generation drugs that attack not the bacteria themselves—which promotes resistance—but rather their cell-to-cell communication with one another. Progress has been slow, however, as bacteria have once again proved more complex than anticipated. But now insights from social evolutionary biology may finally point the way to outsmarting the microbes—by exploiting certain members to undermine the entire group.

Forty years ago scientists discovered that some bacteria send and receive messages—in the form of small molecules—to and from surrounding cells. This kind of communication, called quorum sensing, enables bacteria to monitor their population density and to modulate their behavior accordingly. When there are enough cells around to create a "quorum," bacteria begin producing proteins known as virulence factors that sicken their hosts. They can also grow into aggregates called biofilms that render them up to 1,000 times more resistant to antibiotics.

Quorum sensing is now known to be widespread in the bacterial world, and many researchers hope to develop ways to disrupt it. Kim Janda, a chemical biologist at the Scripps Research Institute in La Jolla, Calif., calls this strategy a "stealth approach." Antibiotics kill bacteria or prevent them from growing, enabling resistant mutants to thrive; drugs that disrupt quorum sensing, on the other hand, would spare the microbes' lives, simply preventing them from causing disease or building biofilms.

The problem is that good quorum-sensing inhibitors have been hard to find. The molecules that bacteria use for communication are often species-specific, so developing universal inhibitors is difficult. Moreover, disruptors found to work well in animals have proved toxic to humans. And some researchers worry that these drugs would be efficacious only at the start of an infection, before a quorum had been reached. As a result of these challenges, few pharmaceutical companies have invested in communication-related drug strategies. "People are a little wary of it," says Helen Blackwell, a chemist at the University of Wisconsin–Madison.

In January, however, University of Edinburgh evolutionary biologist Stuart West and his colleagues announced that they had devised a new idea based on a known quorum-sensing nuance: not all bacteria in a given population communicate normally. So-called signal-blind mutants produce low-level signals but do not respond to them, whereas signal-negative mutants respond to signals but do not produce them.

These cheats still reap the benefits of quorum sensing because their neighbors cooperate, but they conserve a lot of energy relative to their peers. As a result, they thrive and replicate quickly—causing subsequent generations to contain larger and larger proportions of cheats. But once these cheats become too prevalent, communication is so rare that the population cannot reach a quorum, and its overall virulence drops.

West and his colleagues recently infected a group of mice with normal Pseudomonas aeruginosa—a bacterium commonly associated with hospital infections—and infected two other groups with mixtures of half normal Pseudomonas and half signal-blind or signal-negative cheats. Seven days later the mice infected with the mixtures were twice as likely to be alive as compared with the mice infected with normal strains. "It seems crazy, but it's feasible to think that maybe if you've got an infection, you could put in a mutant social cheat," and it could help cure you, West says.

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Such a therapeutic will not be available anytime soon though, West admits. For one thing, it could be difficult for people—let alone regulatory agencies—to accept the idea of treating infections with more bacteria. Still, he and his colleagues have applied for a patent on the concept, and they are also pursuing a related "Trojan horse" idea in which they try to use mutants to introduce specific genes into a population. "Suppose you have an infection, and it's antibiotic-resistant," West explains. "You get a cheat that is susceptible to antibiotics and then let that spread," and soon the population could be treatable with existing drugs.

Even if these particular strategies do not pan out, researchers in the field are confident that more traditional quorum-sensing inhibitors will. Janda, for one, is developing bacterial "vaccines" that help the immune system recognize and eliminate the molecules produced during quorum sensing. He and others—including Princeton University biologist Bonnie Bassler—are also working with a molecule called AI-2 that they believe is used by many types of bacteria as a signaling molecule and thus could be a universal inhibitor. And Blackwell has found hundreds of small molecules that closely but not completely mimic various signaling chemicals; introduced into a population, such molecules could break down communication. "The promise is huge," she says. "We're going forward unabashed."

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