Hacking the bacterial social network: quorum sensing and the future of microbial management

A colony of Paenibacillus dendritiformis, cultivated by the biological physicist Eshel Ben-Jacob. Credit: Wikimedia Commons

Bacteria are social organisms. Over the past 3.5 billion years, they have evolved systems of communication to achieve impressive environmental adaptability—making intelligent community decisions about how best to allocate nutrients, when to sporulate, when to elaborate toxins or invade a human host (Fig. 1) (1,2). For any individual bacterium, the decision to invest in a social program hinges on a simple question. How many of us are here? Within the past twenty years, microbiologists have begun to characterize how signaling couples social behavior to this bacterial census, known as quorum sensing (QS). Their work has revealed a garrulous microbial world around and inside us. It also promises to translate into the biggest advancement in the clinical management of microbes since the discovery of antibiotics. By targeting quorum

sensing and, therefore, social behavior, we will be able to more effectively combat infectious diseases, contain antibiotic resistance, and modify the human microbiome.

In the fight against pathogens, new therapies are badly needed. Since the debut of penicillin in World War II, we have managed to concentrate antibiotic resistance in the most aggressive of human pathogens. The 21st century threatens to become a post-antibiotic era, in which treatment options are increasingly ineffective and everyday infections can kill. Targeting QS is an alternative to what is otherwise an arms race we cannot win. As the military might jam enemy radar, we can use quorum sensing inhibitors (QSI) to disrupt the signals for virulent behavior in pathogens. For example, Staphylococcus aureus, an organism already notorious for antibiotic resistance, effects host damage through the upregulation of its myriad virulence factors, many of which fall under the control of a quorum sensing system called the accessory gene regulator (agr). Recent work in mice shows that a small molecule inhibitor of the agr system can attenuate hemolysin production, decrease tissue injury, and improve immune clearance of S. aureus. Moreover, repeated exposure to the inhibitor does not generate resistance to the therapeutic effects as seen in control treatment with antibiotics (3). These results validate a new target of therapy—not the existence of a single organism per se, but its socially regulated destructive or evasive behavior. Additional QSI candidates are being explored that degrade signaling molecules, inhibit signal synthesis, and block receptors, while target quorum sensing systems are being elucidated in pathogens like Pseudomonas aeruginosa, Streptococcus pneumoniae, and Escherichia coli (4).

One particularly promising application of QSI is the management of chronic biofilms. Biofilms form when bacteria envelop themselves in exopolysaccharides and assume a low metabolic state. Whereas immune cells and antibiotics might otherwise handle a solitary microbe—exposed, enthusiastically reproducing to outcompete neighbors—the cooperative of the biofilm physically shields bacteria from the immune system and undercuts the efficacy of antibiotics, most of which target fast-replicating organisms during division or protein synthesis. Importantly, the inactive appearance of the biofilm belies an internally complex “city of microbes,” heavily dependent on interbacterial communication for its organization (5). This vulnerability is illustrated by QS-

deficient Pseudomonas aeruginosa, which forms abnormal colonies more susceptible to tobramycin and the neutrophil respiratory burst (6). QSI could thus be the key to preventing biofilm formation in human disease, helping to save limbs in diabetics with foot ulcers or prevent chronic lung infection in children with cystic fibrosis. For biofilms that develop on indwelling catheters and prosthetic heart valves, QSI could even be incorporated into the design of the medical device.

Targeting bacterial sociality could also contain the spread of antibiotic resistance. Many genes for antibiotic resistance travel among bacteria on plasmids, transferred along sex pili via conjugation. Conjugation is itself a social behavior, contingent on signaling including QS to coordinate the synthesis of pili with the presence of bacteria nearby (7). There is potential for signal interception—and, loosely speaking, bacterial contraception—at hotbeds of resistance gene transfer. At present, these sites are almost impossible to manage. Resistance plasmid exchange can begin at as little as 1.3% of the minimum inhibitor concentration of antibiotic (8), frustrating efforts to identify and remediate antibiotic contamination in environmental sites, such as water treatment plants and animal husbandry operations. The principles of QSI, however, could sidestep this problem by limiting conjugation and confining the expansion of the bacterial resistome.

A total communications jam is just one approach to manipulating bacterial signaling systems. Signaling molecules are incredibly versatile. In Streptococcus mutans, for example, a single QS peptide can trigger either mass suicide or dormancy in the harsh conditions of the oral cavity, depending on peptide concentration (9). As our understanding of signaling advances, we will want to modify signals at varying intensities to effect a wider variety of desired microbial behavior. This is especially true for the 10 trillion symbionts that comprise our microbiota, whose dysfunction has consequences ranging from metabolic disease to mental illness (10). What proportion of their gene activity might be modifiable with social signaling? Could we enhance colonization resistance on the skin of a vulnerable infant or optimize the metabolic economy of the gut in an obese adult? As we work out the mechanistic basis of our microbiota as an organ system in its own right, targeting bacterial behavior becomes as important as targeting tissue behavior in the heart or liver.

Of course, much work remains to be done. The 20th century experience with antibiotics has taught us humility in dealing with our evolutionary elders, and the world of bacterial communications is promising but complex. The networked nature of bacterial communications will make targeting single species challenging and unpredictable. Like bacteria, however, we are social organisms. Dedicated microbiologists can communicate with clinical investigators at the front line, and together they can translate this unprecedented knowledge of bacterial communications to better human health.

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