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Karina B. Xavier, Ph.D.

Thousands of bacteria are housed in the human gut, and they're a chatty bunch. Biochemist Karina Xavier is eavesdropping on these conversations to understand how bacteria communicate, research that could help her manipulate the conversation to promote healthy guts and healthy people.

The daughter of two scientists, Xavier asked a lot of questions as a child growing up in Portugal. She wanted to understand how nature worked and why, and in school she gravitated toward biology. Xavier found basic physiological processes—like how sugars can become fat—especially captivating. "What I think is really cool is that nature uses the same building blocks to build different structures, so the identification of a particular biological process often leads to the understanding of many others," she says. Not surprisingly, when it came time to pick a major in college, Xavier chose biochemistry.

In 1995, Xavier began her doctoral studies at the Institute for Chemical and Biological Technology (Instituto de Tecnologia Química e Biológica) in Portugal. To learn how certain metabolic pathways evolved, Xavier began her studies with Archaea, ancient single-cell organisms similar to bacteria. Four years later, her Ph.D. complete, Xavier attended a course at Cold Spring Harbor Laboratory in New York, where she met HHMI investigator Bonnie Bassler, a microbiologist at Princeton University studying bacterial signaling. She joined Bassler's team as a postdoctoral researcher in 2000, soon after her new mentor had discovered a molecule involved in bacterial communication. Because the gene that encodes the molecule is present in so many species,

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RESEARCH ABSTRACT

- Interspecies Signaling in Bacterial Communities

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Bassler hypothesized that it might be the way many species of bacteria communicate.

Xavier began investigating the role of this molecule, called AI-2, in the model bacterium *Escherichia coli*. When she mixed *E. coli* with the cholera-causing bacterium *Vibrio cholerae* in a test tube, Xavier found that the two species could use AI-2 to regulate each others' gene expression. "This allowed me to show for the first time that indeed this signal could foster interspecies communication," proving Bassler's hypothesis, Xavier says.

Her study also revealed that when *E. coli* reached high densities, the bacteria began destroying AI-2, which triggered a surprising reaction. AI-2 helps *V. cholerae* sense when their numbers reach a certain density, a function that helps individual bacteria coordinate their actions and their virulence cycles. When *V. cholerae* reach the human gut, the bacteria produce a toxin that causes the watery diarrhea associated with the illness. Without AI-2, the bacteria can't determine their numbers and can no longer regulate the production of virulence factors according to the density of the population.

Why would *E. coli* want to disrupt that communication? The simplest explanation, Xavier says, is that interrupting other species' normal behavior gives *E. coli* a survival advantage. That hypothesis can't be investigated in a test tube, so when Xavier left Bassler's lab in 2006 to create her own research group at the Gulbenkian Science Institute (Instituto Gulbenkian de Ciência) in Portugal, she moved her studies to mice. She and her colleagues are now examining how interspecies signaling works in the guts of mice. For example, Xavier wants to understand what happens when a pathogen like *V. cholerae* invades and how AI-2 signaling affects the balance of beneficial microflora normally present in the gut.

The researchers have created two mutant strains of *E. coli*, one that produces high levels of AI-2 and one that destroys AI-2. The researchers plan to use these mutants to manipulate the signal to see which bacteria thrive and which suffer. "I predict that if you change interspecies communication, you won't have a healthy microbiota," the microorganisms that inhabit the gut, Xavier says. "You will probably be more susceptible to pathogenic infections."

Microbes play a major role in human health. A healthy gut protects against pathogens such as *Clostridium dificile*, a bacterium that causes inflammation and diarrhea (colitis). An unhealthy microbiota, however, has been linked to disease of the bowel, obesity, diabetes, and allergies. A better understanding of the factors that favor one species over another might lead to therapies that can help restore the normal gut flora.

Xavier and her colleagues are also searching for molecules that regulate the virulence of bacteria. Drugs that could destroy these molecules—but not the actual bacterium—might prevent bacteria from causing illness with a lower risk of antibiotic resistance. Xavier looks forward to uncovering many more molecules. In fact, it's her favorite part of the job. "It's fun, but it also leads me to the next step," she says. "It always opens many doors."

Dr. Xavier is Principal Investigator at the Gulbenkian Science Institute (Instituto Gulbenkian de Ciência), Calouste Gulbenkian Foundation, and the Institute for Chemical and Biological Technology (Instituto de Tecnologia Química e Biológica), New University of Lisbon, Portugal.

RESEARCH ABSTRACT SUMMARY:

Karina Xavier studies interspecies cell-to-cell communication in bacteria and its role in beneficial and hostile interactions in the bacterial communities of the mammalian gut. Her aims include establishing strategies to tailor gut microbiota composition and to profit from its protective function against infectious and inflammatory diseases.

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