Podcast Interview: Rob Knight

PNAS: Welcome to Science Sessions. I'm your host Chris Samoray.

The human microbiota consists of the collection of organisms that live on and inside the body. That is organisms like bacteria, viruses, fungi, archaea, and microbial eukaryotes of various kinds, says Rob Knight, who is the Director of the Center for Microbiome Innovation at the University of California, San Diego. Knight is particularly interested in the human gut microbiota, which plays a critical role in regulating the immune response in health and disease. Moreover, a growing body of research points to population differences in gut microbiota in various human autoimmune diseases, including multiple sclerosis. In a PNAS article, Knight and colleagues studied how intestinal bacteria affected the pathogenesis of multiple sclerosis. I spoke with Knight at the 2018 American Association for the Advancement of Science meeting in Austin, Texas. Knight begins by elaborating on the widespread influence of the gut microbiome in the human body.

Knight: We're finding that the gut microbiome is doing a whole lot of stuff beyond what we knew about in terms of its role in digestion. So, some of the other things that it does, it interacts with the liver in terms of things like fatty liver disease and so forth. It interacts with the brain both in positive ways like in modulating anxiety and in negative ways like contributing to different kinds of neurological disease. It interacts with the heart and cardiovascular system in terms of things like atherosclerosis. And essentially what we're finding is that because it's this huge chemical factory that releases many of those chemicals into the bloodstream and also because it has a very intimate connection to our immune system and many of those immune cells also go throughout our bodies, it's having a lot of systemic effects that no one ever suspected until very recently.

PNAS: In the PNAS article, Knight collaborated with a number of colleagues, including Sergio Baranzini, a professor of neurology at the University of California, San Francisco, whose group spearheaded the project, and Sarkis Mazmanian, a MacArthur Fellow and professor of microbiology at Caltech. Knight focused on the DNA sequencing of the microbiomes, but the study was an interdisciplinary and collaborative effort.

The team analyzed the microbiomes of 71 patients with multiple sclerosis and 71 healthy controls. No major differences in microbial community structure were observed among the participants. But the researchers did find larger populations of specific bacteria in the patients compared with the healthy controls. Following the identification of multiple sclerosis-associated bacteria, the researchers transplanted fecal microbiota from the patients into germ-free mice with induced experimental autoimmune encephalomyelitis, or EAE, a mouse model of multiple sclerosis. Knight explains further.

Knight: The study design is first off we need to establish that microbes are associated with MS in humans. So, we looked at some MS patients and matched controls and showed that their microbiomes were different. And then the next step was to ask is that just an association, or maybe MS causes the difference in the microbiome? Or could the microbiome actually be causing MS? There's a mouse model of MS called EAE, and what we show in this paper is that you can transmit the microbiome from humans into mice by transmitting the feces into the mice, and you can induce EAE in the mice that's much worse if they get the microbiome from an MS patient than if they get the microbiome from a healthy control.

PNAS: In essence, mice with microbiota transplants from the patients developed more severe symptoms of EAE than mice with microbiota transplants from the healthy participants. The next step, Knight says, would be to inoculate mice with just the multiple sclerosis-associated bacteria to determine whether those bacteria, rather than all the microbiota present in a fecal transplant, would result in a similar outcome. Knight says the study goes beyond helping to expand understanding of how microbes regulate immunity.

Knight: I think this research is important because it's giving us insight into this part of our bodies that have been largely neglected. For centuries we knew there were a lot of bacteria in there, but everyone assumed that the bacteria were either all the same or that the differences didn't matter except in a few well worked out cases of infectious disease. What we're finding now is that the bacteria contain the vast majority of genes that are associated with our bodies, so, far exceeding the human genome. They're acting as little factories that process our foods, providing not just nutrients but all kinds of chemicals that alter most of how our body works, including drugs that combat other bacteria that they're synthesizing right there in our intestines. I think having a better understanding of these major components of the system that makes us up as a physiological organisms is going to be critical both for reading our current health conditions and for predicting what's going to happen going forward with a particular individual. Understanding what those impacts are and how can we modify our microbiome in low impact but cumulative ways over a lifetime could be amazing for combating some of many chronic diseases that are currently plaguing society.

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