Researchers find link between microbiome, type 1 diabetes

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In the largest longitudinal study of the microbiome to date, researchers from the Broad Institute of MIT and Harvard, Massachusetts General Hospital (MGH), and the DIABIMMUNE Study Group have identified a connection between changes in gut microbiota and the onset of type 1 diabetes (T1D). The study, which followed infants who were genetically predisposed to the condition, found that onset for those who developed the disease was preceded by a drop in microbial diversity - including a disproportional decrease in the number of species known to promote health in the gut. These findings, published by *Cell, Host & Microbe*, could help pave the way for microbial-based diagnostic and therapeutic options for those with T1D.

The human microbiome, which consists of the trillions of microorganisms (bacteria, viruses, and other assorted "bugs") that reside in our bodies, has become an area of growing interest to the medical community as researchers have begun to probe the role it plays in human health and disease. While most bugs in our microbiome are harmless, and even beneficial, changes in the microbiome (and in the interactions microbial species share with their human hosts) have been linked to various disease states, including diabetes and Inflammatory Bowel Disease (IBD).

To explore the possible connection between changes in the microbiome and type 1 diabetes, a team led by Ramnik Xavier, an Institute Member of the Broad and Chief of Gastroenterology at MGH, followed 33 infants (out of a much larger cohort of Finnish and Estonian children)

who were genetically predisposed to T1D. From birth to age 3, the team regularly analyzed the subjects' stool samples, collecting data on the composition of their gut microbiome.

In the handful that developed T1D during this period, the team observed a 25% drop in community diversity (in other words, in the number of distinct species present in the microbiome) one year prior to the onset of the disease. They also noted that this population shift included a decrease in bacteria known to help regulate health in the gut, along with an increase in potentially harmful bacteria that are known to promote inflammation. The findings are further evidence of a previously identified link between inflammation of the gut and type 1 diabetes.

"We know from previous human studies that changes in gut bacterial composition correlate with the early development of type 1 diabetes, and that the interactions between bacterial networks may be a contributing factor in why some people at risk for the disease develop type 1 diabetes and others don't," said Jessica Dunne, Director of Discovery Research at JDRF, which funded the study. "This is the first study to show how specific changes in the microbiome are affecting the progression to symptomatic T1D."

Previous studies have shown that transferring microbiota from mice that were predisposed to autoimmune diabetes (the mouse equivalent of T1D) to mice that were not predisposed increased the prevalence of autoimmune diabetes in mice that were otherwise unlikely to develop the disease. Studies in humans have also shown an association between T1D and the bacterial composition of the gut. However, those studies were retrospective, meaning they were conducted after the patients developed the disease, making causality difficult to prove.

"This study is unique because we have taken a cohort of children at high risk of developing type 1 diabetes and then followed what changes in the

microbiome tip the balance toward progression to the disease," Xavier said.

Aleksandar Kostic, a postdoctoral fellow in Xavier's lab and first author of the study, agreed, calling the study "a compelling piece of evidence pointing toward a direct role of the microbiome in type 1 diabetes."

Since the study also followed infants who did not ultimately develop type 1 diabetes, the researchers were also able to gain insights into the normal development of the microbiome during infancy. They found that, while the species of bacteria present in the gut microbiome vary greatly between individuals, the composition of the microbiome is generally stable within the individual over time.

Moreover, using metabolomic analysis (looking at the metabolites - the tiny molecules produced during metabolism - in subject stool samples), the researchers were also able to see that, while bacterial species varied between individuals, the biological functions served by the various species in the microbiome remained consistent over time, and from person to person.

"Whether the bacterial community is very small, as it is in early infancy, or if it's larger as it is later in life, the community is always serving the same major functions regardless of its composition. No matter which species are present, they encode the same major metabolic pathways, indicating that they're doing the same jobs," Kostic said.

By revealing patterns in the development of the microbiome in healthy individuals, and in those progressing toward T1D onset, the findings may ultimately have diagnostic or therapeutic implications. In terms of diagnostics, understanding how the microbiome shifts prior to the onset of disease could ultimately help clinicians spot early microbial features of T1D.

As for therapeutics, Xavier, who is also the Kurt Isselbacher Chair in Medicine at Harvard Medical School and Co-Director of the Center for Microbiome Informatics and Therapeutics at MIT, says that knowing which species are absent and which are flourishing in the gastrointestinal tract of children with T1D may help make it possible to slow progression of the disease after onset by revealing ways to manipulate the microbiome and, in-turn, microbiome-induced immunoregulation.

The next step, he says, is to broaden the sample pool to determine what factors in the environment and in the microbiome might be making Finns - who are at exceptionally high risk of T1D - more predisposed to the disease than other populations. That includes revisiting the hygiene hypothesis, which holds that a lack of childhood exposure to microbiota and other potentially infectious agents may hinder the development of the immune system and increase susceptibility to immunological disorders.

The researchers are also examining the metagenomic data gathered in the study to determine what biological pathways the microbiota are acting upon - or what metabolites they may be producing - that could be contributing to disease.

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