Development of gut microbes and gut immunity linked

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Studying twins, scientists have described how the gut's immune system and the gut's resident microbes co-develop. Credit: Washington University in St. Louis

Studying twins from birth through age 2, scientists at Washington University School of Medicine in St. Louis have shown that the gut's

immune system develops in sync with the gut's tens of trillions of microbes. The findings have implications for understanding the underpinnings of healthy growth and, potentially, the origins of various immune disorders such as inflammatory bowel disease, food allergies, and malnourished children's poor responses to oral vaccination.

Published May 25 in the journal *Nature*, the study included data collected from 40 healthy twin pairs living in the St. Louis metro area. It also included data from germ-free mice, so-called because they lack gut microbes of their own. These mice received transplants of gut microbes from two of the pairs of twins. The studies allowed the researchers to analyze the effects of age, genetics, diet and other environmental factors—such as whether the babies were born vaginally or by C-section—upon formation of the gut's immune system and its microbial community, known as the microbiota.

"This study provided us with a way to measure how the gut microbiota and the immune system co-develop in healthy infants and children," said senior author Jeffrey I. Gordon, MD, the Dr. Robert J. Glaser Distinguished University Professor and director of Washington University's Center for Genome Sciences & Systems Biology. "If we can understand how these two systems interact normally, we can begin to identify disruptions in these interactions during a critical period of development after birth, and how such disruptions may lead to disease. Ultimately, the goal is to devise ways to support healthy coordinated development of both systems."

The microbes that dwell inside the gut have important jobs, such as making vitamins and processing nutrients. Gordon describes the community of bacteria in the gut as a microbial "organ" that must develop alongside the body's other tissues, organs and systems. To enable the microbiota to perform its many tasks, the gut must have an effective barrier that keeps the resident bacteria from invading other parts of the

body and that doesn't launch a chronic immune attack against these beneficial microbes.

Past work by Gordon's team has helped to define the normal development of the gut microbiota. Studying infants and young children in Bangladesh, Malawi and now St. Louis, the researchers have identified elements of gut microbial community development that are shared by healthy children in different geographic regions, despite their differing diets. The studies have demonstrated that malnutrition is likely caused, at least in part, by an immature gut microbial community that fails to develop normally.

For the current study, Gordon and his colleagues studied identical and fraternal twins, which allowed the researchers to make comparisons between closely related individuals living in the same homes, and then across families as the children grew.

The researchers assessed how the gut's immune system developed by measuring how one of its most prominent antibodies, immunoglobulin A (IgA), interacts with members of the developing gut bacterial community. By defining which bacteria in the microbiota were and were not targeted by IgA, the researchers were able to mark the different stages of maturation of the gut's immune system.

Gordon and his team demonstrated that IgA binds to some of the bacterial strains present in the developing microbiota but not to others. They also showed that this pattern of IgA "targeting" is not simply a reflection of changing patterns of abundance of these strains in the maturing microbial community. Studying the gut microbes early in the babies' lives, they found that the pattern of IgA targeting of bacteria was very different between families but subsequently evolved toward a shared "program" of IgA targeting during the second year of babies' lives. Being an identical as opposed to a fraternal twin had only modest

effects on the degree of similarity in IgA targeting of bacteria as infants grew.

Seeking to identify factors beyond human genetics that might control targeting, the researchers transplanted gut microbiota samples, obtained from two pairs of twins at 6 and 18 months of age, into young germ-free mice. They fed the mice a sequence of diets simulating the transition from milk feeding to solid foods and, for comparison sake, back to exclusive milk feeding. The age-specific patterns of IgA targeting of bacteria seen in the twins were reproduced in the animal model. Moreover, some but not most of the IgA responses were affected by the diet switches, suggesting that diet plays some role, but that intrinsic properties of bacteria—such as their surface features—are larger players in governing their targeting by the gut immune system.

Gordon's group currently is determining whether the shared program of normal maturation of gut IgA responses in these twins applies to infants and children living in different regions of the world, including areas where malnutrition is rampant.

The study also suggests a novel way that gut immunity could malfunction. While some individuals may simply lack a sufficient quantity of IgA, others may have previously unappreciated IgA deficiencies that come in the form of abnormal patterns of IgA targeting to gut bacteria.

"The question is whether deviations from the normal pattern of development of the gut microbiota and gut IgA responses could result in increased risk of infection with bacteria that cause diarrhea, the impaired responses to vaccination commonly associated with malnutrition, or breakdown in the biological barriers that separate us from foreign as well as resident microbes," Gordon said.

More information: Joseph D. Planer et al. Development of the gut microbiota and mucosal IgA responses in twins and gnotobiotic mice, *Nature* (2016). DOI: 10.1038/nature17940