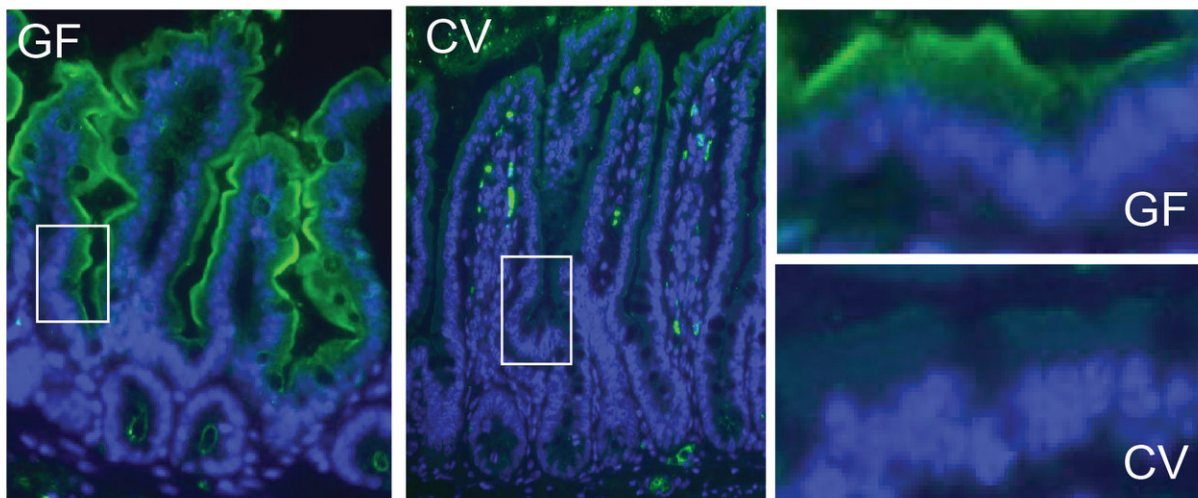


Gut microbiome regulates the intestinal immune system, researchers find

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Brown researchers found that the amount of vitamin A-converting protein, shown in green, varied between the guts of normal mice (CV) and mice without gut bacteria (GF). Credit: Vaishnava Lab/Immunity

Scientists have long known that bacteria in the intestines, also known as the microbiome, perform a variety of useful functions for their hosts, such as breaking down dietary fiber in the digestive process and making vitamins K and B7.

Yet a new study unveils another useful role the microbiome plays. A team of researchers from Brown University found that in mice, the gut

microbiome regulates the host's immune system—so that rather than the host's defense system attacking these [helpful bacteria](#), the bacteria can co-exist peacefully with the immune system.

What's the trick to the microbiome's work with the immune system? Vitamin A—the bacteria moderate active [vitamin](#) A levels in the intestine, protecting the microbiome from an overactive immune response.

That insight may prove important for understanding and treating autoimmune and [inflammatory diseases](#), said Shipra Vaishnava, an assistant professor of molecular microbiology and immunology at Brown.

"A lot of these diseases are attributed to increased immune response or immune activation, but we've found a new way that bacteria in our gut can dampen the immune response," Vaishnava said. "This research could be critical in determining therapies in the case of autoimmune diseases such as Crohn's disease or other inflammatory bowel diseases, as well as vitamin A deficiency."

The study was published on Tuesday, Dec. 18, in the journal *Immunity*.

Microbiomes of mice and men

The gut microbiome is an ecosystem made of 100 trillion bacteria that have evolved to live in the special conditions of the intestines, Vaishnava said. The vast majority of these bacteria do not harm their hosts but are helpful instead. A healthy microbiome, just like a healthy forest, has many species co-existing together and can fend off hostile intruders—such as disease-causing bacteria or invasive species.

In both humans and mice, the phyla Firmicutes and Bacteroidetes

comprise the majority of the gut microbial community. To play their part in regulating their hosts' immune systems, the bacteria in the microbiome fine-tune the levels of a protein responsible for the conversion of vitamin A to its active form in their hosts' gastrointestinal tract, the researchers found.

Vaishnava's team found that Firmicutes bacteria, particularly members of the class Clostridia, reduce the expression of a protein within the cells that line the intestines. The protein, retinol dehydrogenase 7 (Rdh7) converts dietary vitamin A to its active form, retinoic acid, Vaishnava said. The Clostridia bacteria, common to both mice and men, also promote increased vitamin A storage in the liver, the team found.

Vaishnava expects the findings are generalizable to the interactions between the human microbiome and their hosts as well.

Mice genetically engineered to not have Rdh7 in their intestinal cells have less retinoic acid in the intestinal tissue, as the researchers expected. Specifically, the guts of the engineered mice had fewer immune cells that make IL-22, an important cellular signal that coordinates the antimicrobial response against gut bacteria. Other components of the immune system such as cells with immunoglobulin A and two types of T-cells were the same as in standard mice, suggesting Rdh7 is only essential for the regulating antimicrobial response, Vaishnava said.

The researchers do not know exactly how Rdh7 is suppressed, but Clostridia bacteria are known to produce short chain fatty acids that change host gene expression. As a next step in their research, the team will study how bacteria regulate Rdh7 expression, including examining various short chain fatty acids, Vaishnava said.

In addition, the team will conduct research to understand why Rdh7

suppression is critical. They are working to genetically engineer mice to always express Rdh7 in their intestinal cells. Vaishnava wants to see how this affects the mouse microbiome and if it leads to any inflammation or autoimmune disease-like conditions for the mice. They will also explore the impacts of increased vitamin A storage in the liver due to bacteria Rdh7 regulation, Vaishnava said.

Helping human health

The researchers say that understanding how bacteria regulate the immune system's responses could be important in unlocking the keys to disorders like Crohn's disease.

Data from clinical studies has shown that inflammation in the bowel is a result of disrupted interactions between a host and their [gut microbiome](#), Vaishnava said.

"The role of vitamin A in inflammation is context-dependent and is very hard to tease apart," Vaishnava said. "A change in vitamin A status and vitamin A metabolic genes coincides with inflammatory bowel diseases, but we don't know if this promotes inflammation or not. We hope that adding our finding—that bacteria can regulate how vitamin A is being metabolized in the intestine or stored—could help clarify why the field is seeing what it is seeing."

These findings could also provide clues about the importance of the [microbiome](#) in addressing vitamin A deficiency, a problem that is particularly prevalent in Africa and Southeast Asia.

Vitamin A deficiency affects approximately one third of children under the age of five, according to the World Health Organization (WHO). Vitamin A deficiency weakens the [immune system](#) and increases the risk of infectious diseases. The WHO has been providing at-risk children

with vitamin A supplements for the past 25 years, but it hasn't been as successful as hoped for, according to Vaishnava. This study shows bacteria are a big part of vitamin A absorption and storage and perhaps children need to have the right combination of bacteria in the gut in order for the vitamin A supplements to be most effective, she added.

"Both our diet and the bacteria in our gut are critically linked in regulating how our immune cells behave," Vaishnava said. "Finding what those links are at a molecular level is important to figuring out how we could use either diet or [bacteria](#), or both of them together, to have a therapeutic effect in inflammatory or infectious diseases."

More information: Mayara Grizotte-Lake et al, Commensals Suppress Intestinal Epithelial Cell Retinoic Acid Synthesis to Regulate Interleukin-22 Activity and Prevent Microbial Dysbiosis, *Immunity* (2018). [DOI: 10.1016/j.immuni.2018.11.018](https://doi.org/10.1016/j.immuni.2018.11.018)

Provided by Brown University

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