Immune system cells in the gut linked to stress-induced depression

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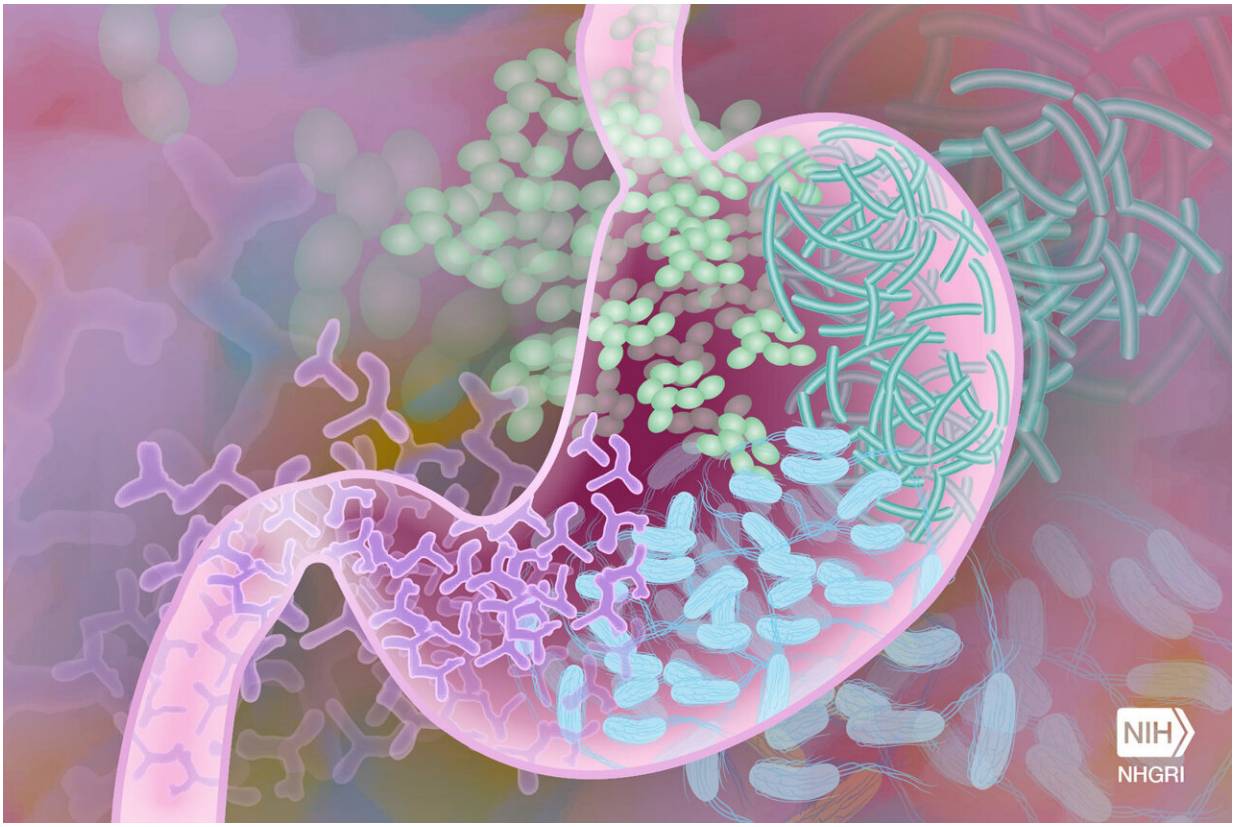

Illustration of bacteria in the human gut. Credit: Darryl Leja, National Human Genome Research Institute, National Institutes of Health

In experiments with mice and humans, a team led by Johns Hopkins Medicine researchers says it has identified a particular intestinal immune

cell that impacts the gut microbiome, which in turn may affect brain functions linked to stress-induced disorders such as depression. Targeting changes mediated by these immune cells in the gut, with drugs or other therapies, could potentially bring about new ways to treat depression.

The findings of the study were published March 20, 2023 in the journal *Nature Immunology*.

"The results of our study highlight the previously unrecognized role of intestinal gamma delta T cells (γδ T cells) in modifying psychological stress responses, and the importance of a protein receptor known as dectin-1, found on the surface of immune cells, as a potential therapeutic target for the treatment of stress-induced behaviors," says Atsushi Kamiya, M.D., Ph.D., professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine and the study's senior author.

Dectin-1 binds to certain antigens, or proteins, to signal immune cells to activate in specific ways. This receptor, the researchers say, may be involved in the microbiome alteration and immune-inflammatory responses in the colon of mice, which suggests that it may be involved in stress responses via γδ T cells in the intestinal immune system.

On the basis of previous studies suggesting that immune inflammatory responses in the gut are related to depression, Kamiya and his team designed experiments to focus on understanding stress-induced behaviors produced by an imbalance in the gut microbiota—types of microorganisms found in a specific environment, such as bacteria, fungi and viruses.

To this end, the team examined the effects of chronic social defeat stress (CSDS) on the gut microbiota in mice. CSDS is a standard rodent test to

study stress-induced disorders such as depression. In a series of experiments, the researchers simulated potential stress inducing environments that could mimic similar responses in human environments. After each exposure, the mice were assessed and classified as stress-resilient (stress did not diminish social interactions) or stress-susceptible (stress increased social avoidance).

Fecal samples were then collected and put through genetic analysis to identify the diversity of bacteria in the gut microbiota of the mice. The analysis showed that the intestinal organisms were less diverse in stress-susceptible mice than in stress-resilient mice. It specifically revealed that there were less Lactobacillus johnsonii (L. johnsonii)—a type of probiotic, or "good" bacteria—in stress-susceptible mice compared to stress-resilient mice.

"We found that stress increased the γδ T cells, which in turn increased social avoidance," says Xiaolei Zhu, M.D., Ph.D., assistant professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine and the study's lead author. "However, when the stressed mice were given L. johnsonii, social avoidance decreased and the γδ T cells went to normal levels, suggesting that CSDS-induced social avoidance behavior may be the result of lower levels of the bacteria and γδ T cell changes."

Looking for potential natural approaches for prevention of depression rooted somehow in the gut, the researchers explored how changes in dectin-1 on CSDS-induced elevation of γδ T cells responded to pachyman. A compound extracted from wild mushrooms, pachyman is used as a natural anti-inflammatory agent and for treating depression in Eastern medicine.

For this experiment, mice were fed a dose of pachyman, which was shown in previous research to affect immune function. Data from flow

cytometry analysis—a technology used to measure the physical and chemical characteristics of a population of cells—provided evidence that dectin-1 binds to pachyman, inhibiting CSDS-induced γδ17 T cell activity and easing social avoidance behavior.

To gain insight into how the alterations in the gut microbiota could impact the human brain, the researchers investigated the makeup of gut organisms in people with major depressive disorder (MDD) compared to people without MDD. From June 2017 to September 2020, 66 participants, ages 20 or older, were recruited at Showa University Karasuyama Hospital, Keio University Hospital and Komagino Hospital in Tokyo, Japan. Of the study participants, 32 had MDD (17 women and 15 men). The other 34 participants (18 women and 16 men) who did not have MDD formed the control group.

Stool samples were collected from all study participants, who had comprehensive evaluations including psychiatric history and standard screening assessments for depression and anxiety. In these assessments, higher scores indicate greater depressive symptoms. Genetic analysis of the stool samples showed no difference in the diversity of intestinal bacteria between the subjects with MDD and the control group. However, the relative abundance of Lactobacillus was inversely related to higher depression and anxiety scores in the MDD group, meaning that the more Lactobacillus found in the gut, the lower the potential for depression and anxiety, the researchers say.

"Despite the differences of intestinal microbiota between mice and humans, the results of our study indicate that the amount of Lactobacillus in the gut may potentially influence stress responses and the onset of depression and anxiety," says Kamiya.

The investigators say more research is needed to further understand how γδ T cells in the intestinal immune system may impact the neurological

functions in the brain and the role of dectin-1 in other cell types along the gut-brain connection under stress conditions.

"These early-stage findings show that, in addition to probiotic supplements, targeting drugs to such types of receptors in the gut immune system may potentially yield novel approaches to prevent and treat stress-induced psychiatric symptoms such as depression," says Kamiya.

More information: Atsushi Kamiya, Dectin-1 signaling on colonic γδ T cells promotes psychosocial stress responses, *Nature Immunology* (2023). DOI: 10.1038/s41590-023-01447-8.
www.nature.com/articles/s41590-023-01447-8

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