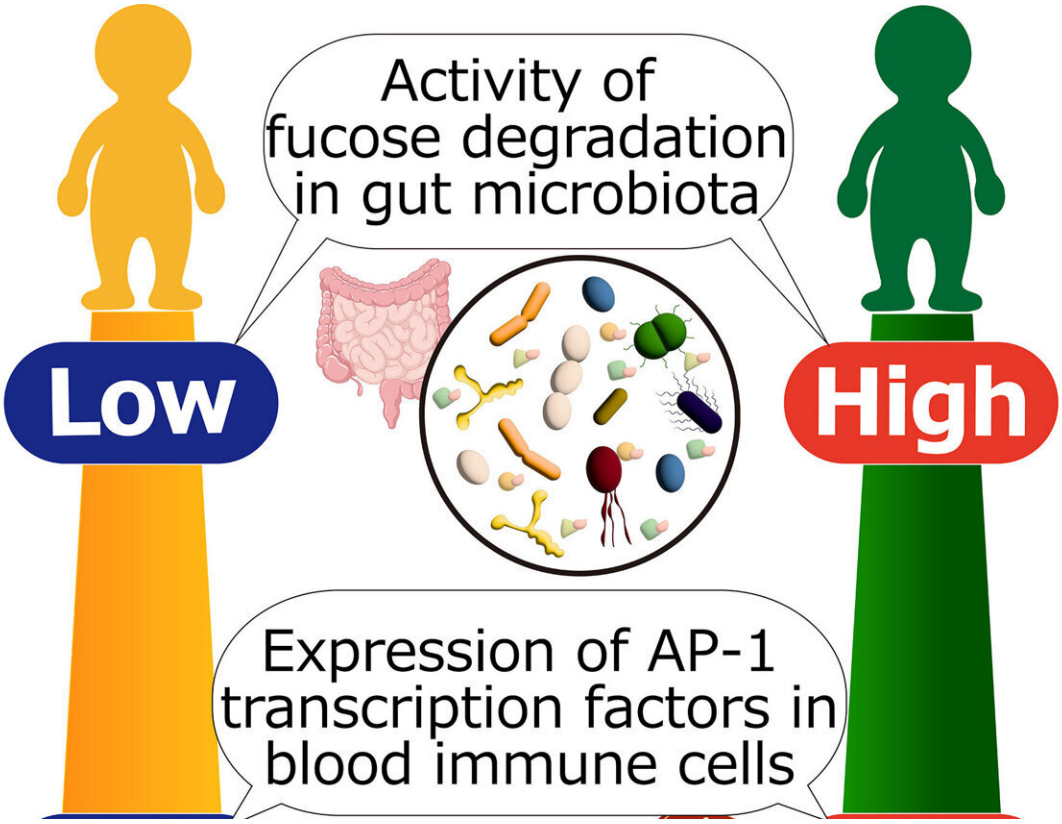
Gut bacteria could be behind weaker immune responses to COVID-19 vaccine

April 20 2023



High activity of fucose digestion by bacteria in the gut is associated with higher expression of two AP-1 transcription factors, FOS and ATF3 in blood immune cells, and with a lower T-cell response to the COVID-19 vaccine. Credit: Okinawa Institute of Science and Technology (OIST)

Gut bacteria that break down a sugar called fucose could be dampening

our immune response to the COVID-19 mRNA vaccine, according to a study led by researchers from the Okinawa Institute of Science and Technology (OIST).

The scientists report that increased fucose digestion by bacteria in the gut before vaccination was associated with lower numbers of T-cells activated by vaccination. T-cells are an important type of blood immune cell that are activated by a specific strain of bacteria or virus, and then multiply to fight the infection.

The findings, published April 20 in *Communications Biology*, illustrate the important impact that the trillions of bacteria in our gut—collectively called our 'gut microbiome'— have on our immune health and adds a missing piece to the puzzle of why vaccination varies in effectiveness from person to person.

"Not everyone who gets the same vaccine receives an equal level of protection, but we still don't really understand why people respond so differently," said Professor Hiroki Ishikawa, who leads the OIST Immune Signal Unit. "If we can get to the bottom of what causes this variation, we could predict how an individual might respond to a vaccine, and perhaps find new strategies to promote the immune response."

While this research focused on the response to the COVID-19 Pfizer mRNA vaccine, the researchers believe their results could also be relevant for other mRNA vaccines in development that protect against other infectious diseases, and even cancer.

In this study, Prof. Ishikawa and his colleagues took a stool sample and multiple blood samples from 96 healthy participants living in Okinawa, starting before the first dose of the vaccine, and ending a month after the second dose.

They then did a broad analysis, looking at all the genes from immune cells in the blood and bacteria in the gut to see if there was any association with an individual's T-cell and antibody levels.

The researchers did not find a significant link to antibody levels, but they did find that individuals that had a lower T-cell response also had a gut microbiome with a high activity of fucose digestion.

The team also found that individuals with a reduced T-cell response had higher expression of two genes, FOS and ATF3, prior to vaccination. These genes are expressed by blood immune cells, and code for proteins that are part of a larger group, called AP-1 transcription factors. Previous research has shown that different AP-1 transcription factors control T-cell survival and activity, but the exact role and function of these two proteins remains unknown.

Individuals with higher expression of FOS and ATF3 prior to vaccination also had microbiomes with high activity of fucose digestion, suggesting that the gut's impact on the immune system is through a pathway that involves FOS and ATF3.

"The mechanism is not yet proven, but we propose that fucose digestion leads to increased baseline expression of FOS and ATF3 in blood immune cells, which in turn weakens the response to the COVID-19 vaccine," said Masato Hirota, first author and Ph.D. student in the Immune Signal Unit. "It's clear that the gut bacteria have an important impact on the overall health of the immune system."

The team now plans to experimentally manipulate the gut bacteria in mice and investigate the exact mechanism of FOS and ATF3, to further understand the link between the microbiome, blood immune cells and the overall immune response.

More information: Human immune and gut microbial parameters associated with inter-individual variations in COVID-19 mRNA vaccine-induced immunity, *Communications Biology* (2023). DOI: 10.1038/s42003-023-04755-9

Provided by Okinawa Institute of Science and Technology