Studies find that microbiome changes may be a signature for myalgic encephalomyelitis/chronic fatigue syndrome

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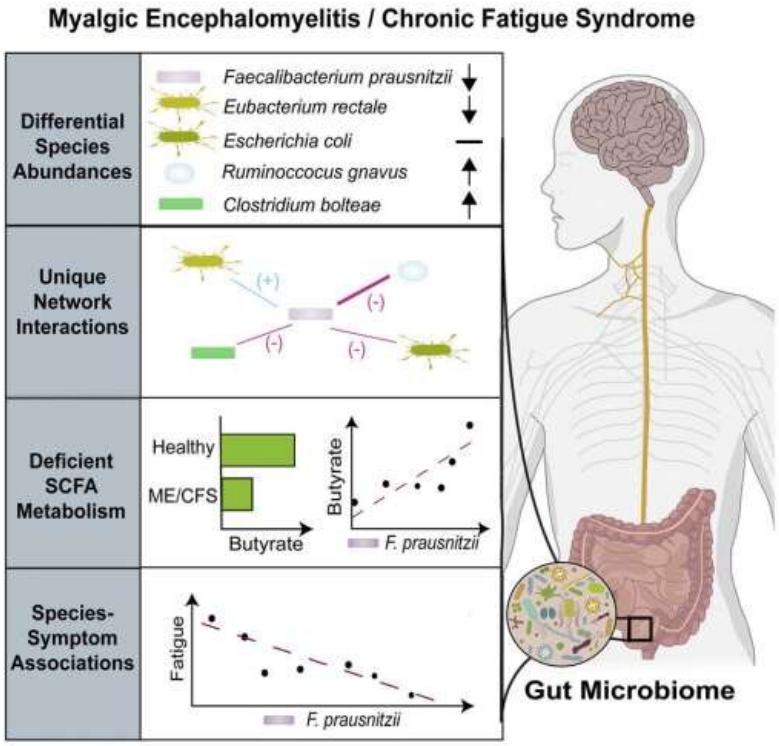


Graphical abstract. Credit: *Cell Host & Microbe* (2023). DOI: 10.1016/j.chom.2023.01.004

Researchers have found differences in the gut microbiomes of people

with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) compared to healthy controls. Findings from two studies, published in *Cell Host & Microbe* add to growing evidence that connects disruptions in the gut microbiome, the complete collection of bacteria, viruses, and fungi that live in our gastrointestinal system, to ME/CFS.

"The microbiome has emerged as a potential contributor to ME/CFS. These findings provide unique insights into the role the microbiome plays in the disease and suggest that certain differences in gut microbes could serve as biomarkers for ME/CFS," said Vicky Whittemore, Ph.D., program director at NIH's National Institute of Neurological Disorders and Stroke (NINDS).

ME/CFS is a serious, chronic, and debilitating disease characterized by a range of symptoms, including fatigue, post-exertional malaise, sleep disturbance, cognitive difficulties, pain, and gastrointestinal issues. The causes of the disease are unknown and there are no treatments.

In one study, senior author Brent L. Williams, Ph.D., assistant professor, W. Ian Lipkin, M.D., John Snow Professor of Epidemiology and director of the Center for Infection and Immunity at the Columbia University Mailman School of Public Health, in New York City, and their collaborators analyzed the genetic makeup of gut bacteria in fecal samples collected from a geographically diverse cohort of 106 people with ME/CFS and 91 healthy controls. The results revealed key differences in microbiome diversity, quantity, metabolic pathways, and interactions between species of gut bacteria.

Dr. Williams and his colleagues found that people with ME/CFS had abnormally low levels of several bacterial species compared to healthy controls, including Faecalibacterium prausnitzii (F. prausnitzii) and Eubacterium rectale. These health-promoting bacteria produce a short chain fatty acid called butyrate, a bacterial metabolite, or by-product,

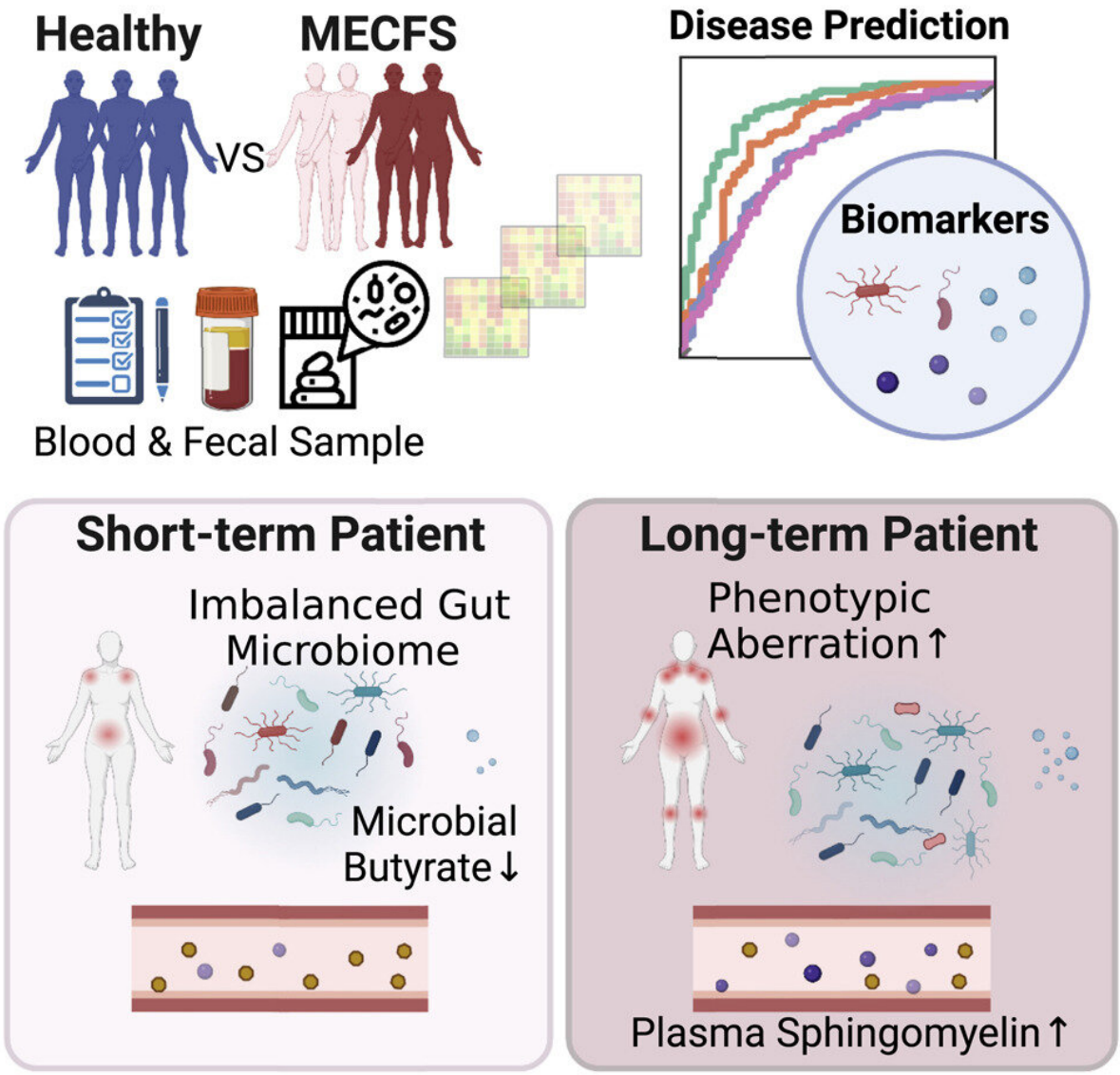
that plays an important role in maintaining gut health. An acetate-producing bacterium was also reduced in samples obtained from people with ME/CFS.

More detailed metabolomic analyses confirmed that a reduction in these bacteria was associated with reduced butyrate production in ME/CFS. Butyrate is the primary energy source for cells that line the gut, providing up to 70% of their energy requirements, support for the gut immune system, and protection against diseases of the digestive tract. Butyrate, tryptophan, and other metabolites detected in the blood are important for regulating immune, metabolic, and endocrine functions.

While species of butyrate-producing bacteria decreased, there were increased levels of nine other species in ME/CFS, including Enterocloster bolteae and Ruminococcus gnavus, which are associated with autoimmune diseases and inflammatory bowel disease, respectively.

Dr. Williams' group also reported that an abundance of F. prausnitzii was inversely associated with fatigue severity in ME/CFS, suggesting a possible link between gut bacteria and disease symptoms. More research is needed to determine if differences in the gut microbiome are a consequence or cause of symptoms.

The findings indicate that imbalances in these 12 species of bacteria could be used as biomarkers for ME/CFS classification, potentially providing consistent, measurable targets to improve diagnosis.



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The gut microbiome is an ecosystem with complex interactions between bacteria, where microbes can exchange or compete for nutrients, metabolites, or other molecular signals. Researchers found notable

differences in the network of species interactions in people with ME/CFS—including unique interactions between F. prausnitzii and other species. This indicates that there is an extensive rewiring of bacterial networks in ME/CFS.

"In addition to differences in individual species in ME/CFS, focusing a lens on community interaction dynamics may add greater specificity to the broad definition of dysbiosis, distinguishing between other diseases in which the gut microbiome becomes imbalanced," said Dr. Williams. "This is also important for generating new testable hypotheses about the underlying mechanisms and mediators of dysbiosis in ME/CFS and may eventually inform strategies to correct these imbalances."

A balanced microbiome is also essential for a variety of neural systems, especially immune regulation and coupling between energy metabolism and blood supply in the brain, as well as the function of the nerves that supply the gut.

In another study at the Jackson Laboratory in Farmington, Connecticut, Julia Oh, Ph.D., associate professor, and Derya Unutmaz, M.D., professor, teamed up with other ME/CFS experts to study microbiome abnormalities in different phases of ME/CFS. Dr. Oh's team collected and analyzed clinical data, fecal samples, and blood samples from 149 people with ME/CFS who had been diagnosed within the previous four years (74 short-term) or who had been diagnosed more than 10 years ago (75 long-term) and 79 healthy controls.

The results showed that the short-term group had less microbial diversity, while the long-term group established a stable, but individualized gut microbiome similar to healthy controls. Dr. Oh and her colleagues found lower levels of several butyrate-producing species, including F. prausnitzii, especially in the short-term participants. There was also a reduction in species associated with tryptophan metabolism in

all ME/CFS participants compared to controls.

Dr. Oh's group also collected detailed clinical and lifestyle data from participants. By combining these data with genetic and metabolome data, the team developed a way to accurately classify and differentiate ME/CFS from healthy controls. Using this approach, they found that individuals with long-term ME/CFS had a more balanced microbiome but showed more severe clinical symptoms and progressive metabolic irregularities compared to the other groups.

Both studies identify potential biomarkers for ME/CFS, which may inform diagnostic tests and disease classification. Understanding the connection between disturbances in the gut microbiome and ME/CFS may also guide the development of new therapeutics.

Additional research is required to learn more about the pathophysiological implications of butyrate and other metabolite deficiencies in ME/CFS. Future studies will determine how gut microbe disturbances contribute to symptoms, including changes during disease progression.

Both studies appeared in *Cell Host & Microbe*.

More information: Cheng Guo et al, Deficient butyrate-producing capacity in the gut microbiome is associated with bacterial network disturbances and fatigue symptoms in ME/CFS, *Cell Host & Microbe* (2023). DOI: 10.1016/j.chom.2023.01.004

Ruoyun Xiong et al, Multi-'omics of gut microbiome-host interactions in short- and long-term myalgic encephalomyelitis/chronic fatigue syndrome patients, *Cell Host & Microbe* (2023). DOI: 10.1016/j.chom.2023.01.001

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