New findings from Human Microbiome Project reveal how microbiome is disrupted during IBD

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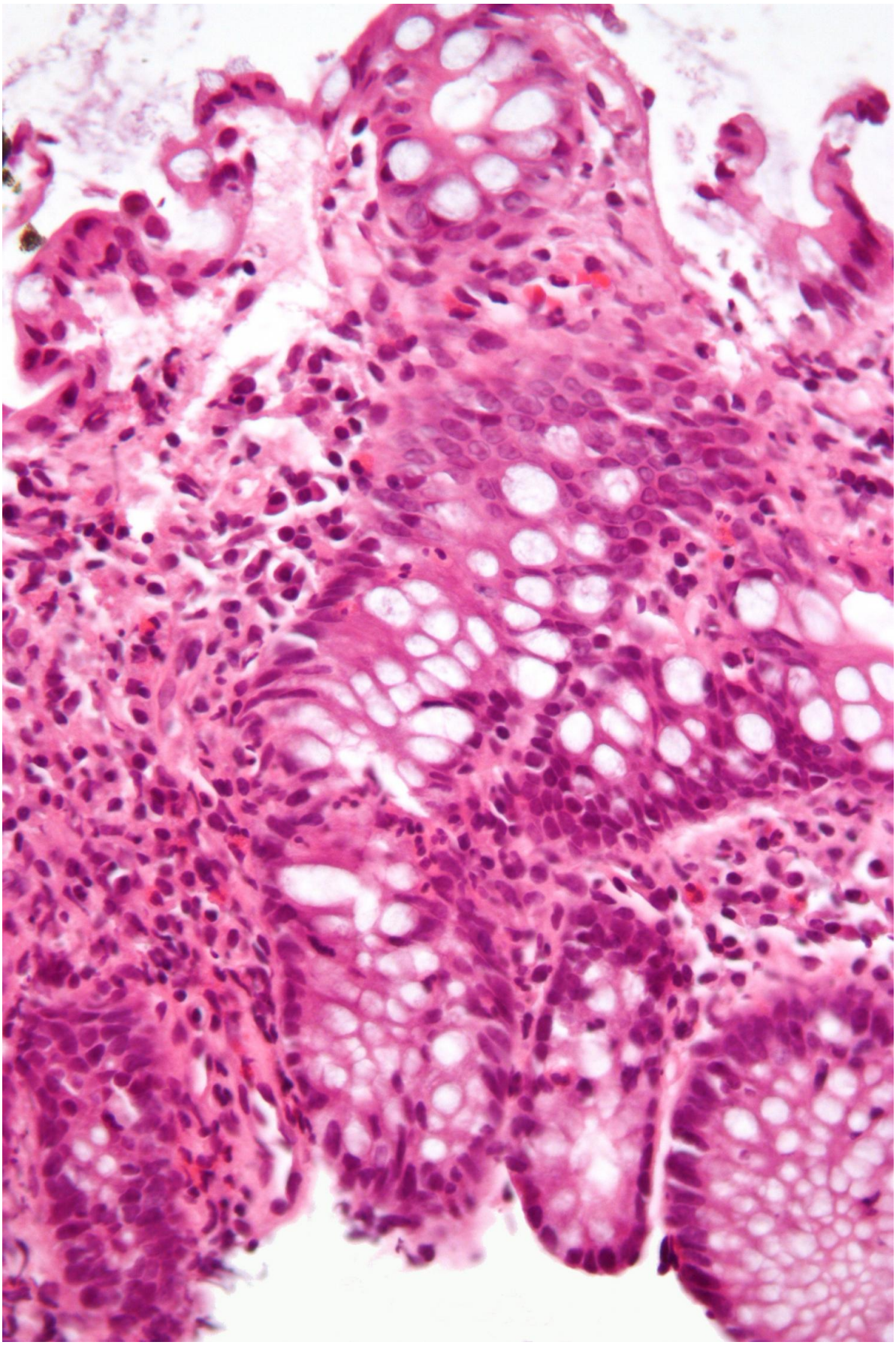

Micrograph showing inflammation of the large bowel in a case of inflammatory bowel disease. Colonic biopsy. Credit: Wikipedia/CC BY-SA 3.0

A new study led by researchers from Harvard T.H. Chan School of Public Health and the Broad Institute of MIT and Harvard is the first to have observed the complex set of chemical and molecular events that disrupt the microbiome and trigger immune responses during flare-ups of inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis.

While previous studies have cataloged microbial changes during IBD, the researchers in this study developed a unique biotechnology toolbox to understand why microbiomes change during IBD and how this provokes an unhealthy inflammatory reaction. These tools allowed them to measure microbial chemical changes and human gene regulatory shifts, potentially allowing for new therapies in the future.

The study, which included dozens of collaborators, was part of the second phase of the Human Microbiome Project (HMP). The project, the first phase of which was launched in 2007 by the National Institutes of Health (NIH) Common Fund, aimed to characterize the microbiome in healthy adults and in people with specific microbiome-associated diseases. The most recent phase of work began in 2013 with support from across the NIH, and with the mandate to tease apart the molecular mechanisms underlying the microbiome's roles in disease.

"The Human Microbiome Project overall has been a flagship effort in understanding the microbiome's contributions to health, and in creating a community of researchers who can study the microbiome to discover

new diagnostics and therapies for disease," said Curtis Huttenhower, professor of computational biology and bioinformatics at Harvard Chan School and associate member at the Broad Institute and senior author of the study. "Our results from this study pave the way for early detection of upcoming flares in disease activity—which can then be aggressively treated—or potentially for new biochemical therapeutic opportunities to encourage complete remission of IBD."

The finding will be published May 29, 2019 in *Nature*.

The gut microbiome is a community of trillions of microbes, including bacteria, viruses, and fungi. Each person has a distinct microbiome, and research indicates that the microbiome plays an important role in numerous diseases, including IBD, which affects more than 3.5 million people worldwide and is growing in prevalence. IBD is a chronic disease that is marked by periods of remission followed by flare-ups in which the disease becomes active.

For this study, the most comprehensive analysis to date of human microbiome interactions during IBD, researchers followed 132 participants for one year and compared Crohn's disease and ulcerative colitis patients to a control group of participants that did not have IBD. Participants provided stool samples every two weeks, blood samples approximately once a quarter, and a set of colon biopsies at the start of the study for analysis. In total, 2,965 stool, biopsy, and blood samples were analyzed with an unprecedented suite of molecular, cellular, and clinical tools to understand the detailed biochemistry of the disease.

First, these detailed measurements made it easy to observe and confirm findings from previous studies, such as a reduction in overall gut ecological diversity and the gain and loss of specific "pro-" and "anti-inflammatory" microbes during disease.

More importantly, the suite of tools deployed for this study allowed researchers to determine the reasons for the changes. The results showed that during periods of disease activity, people with IBD had fewer microbially-derived chemicals, which they speculated could be due to a combination of factors, including less beneficial microbial metabolism, poorer nutrient absorption, greater water or blood levels in the bowels, and more urgent bowel movements. These factors decreased the overall stability of the gut microbial ecosystem, leading to more episodes of improper immune responses and overreaction to the normal gut microbiome among IBD patients.

Specifically, during periods of disease activity people with IBD had higher levels of polyunsaturated fatty acids, including adrenate and arachidonate. The researchers also discovered that nicotinuric acid was found almost exclusively in the stool of patients with IBD and that levels of vitamins B5 and B3 were particularly depleted in the gut of people with IBD.

The team also found that bile acids—a set of compounds made by humans but chemically modified by gut microbes—were disrupted during IBD as well, in tandem with molecular regulation in groups of microbes. These included a group of bacteria related to the genus Subdoligranulum that are carried by almost everyone, but are depleted during inflammation, and which have not been previously isolated or characterized.

Overall, the findings provide the most detailed snapshot to date of the microbiome in people with IBD, during active and non-active disease states. The findings showed that different forms of IBD—Crohn's disease compared with ulcerative colitis, for instance—had different effects on the activity and composition of the microbiome. The researchers said the findings provide promising new targets for potential IBD treatments, including polyunsaturated fatty acids, bile acid

derivatives, and human immune response pathways, as well as new data, tools, and protocols that will enable future research on IBD and the microbiome.

"Given how tightly connected the microbiome is with our health and wellbeing, these results shed some light on how we might avoid the problems that arise when this relationship goes awry, and how we might be better stewards of these life-long companions," said Jason Lloyd-Price, who worked on the study while a research scientist at Harvard Chan School and the Broad Institute and was lead author of the paper.

More information: Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases, *Nature* (2019). DOI: 10.1038/s41586-019-1237-9 , www.nature.com/articles/s41586-019-1237-9

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