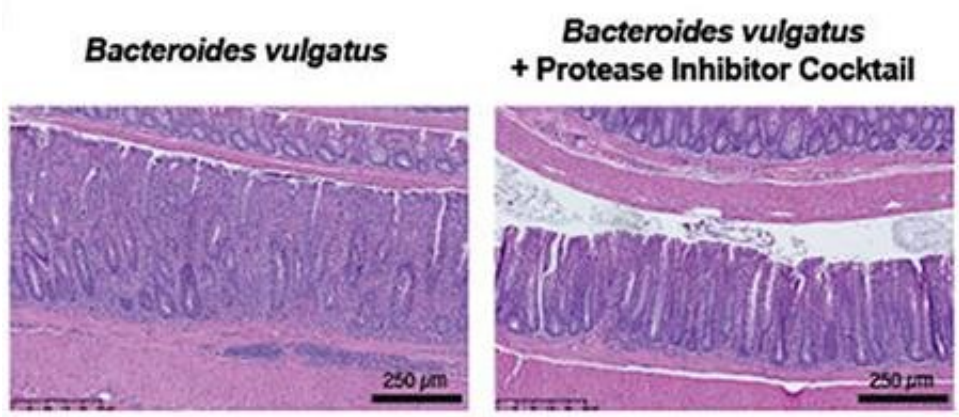
Stool samples reveal microbial enzyme driving bowel disease

January 28 2022, by Nicole Mlynaryk



The presence of Bacteroides vulgatus led to colitis in the mouse colon (left). However, protease inhibition protected the walls of the colon and reduced influx of inflammatory cells (right). Credit: University of California - San Diego

Ulcerative colitis, a subtype of inflammatory bowel disease, is a chronic ailment of the colon affecting nearly one million individuals in the United States. It is thought to be linked to disruptions in the gut microbiome—the bacteria and other microbes that live inside us—but no existing treatments actually target these microorganisms.

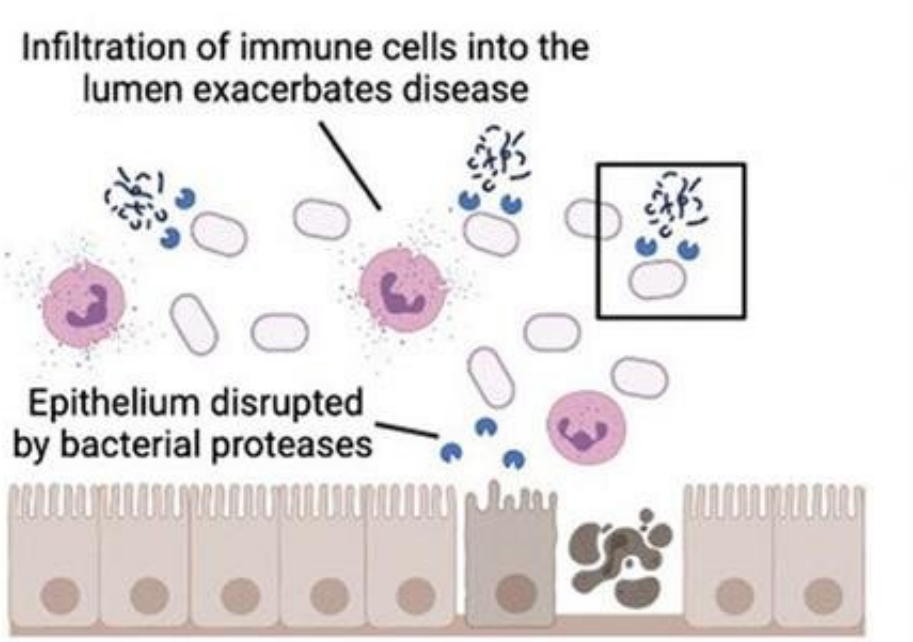
In a study publishing on January 27, 2022 in *Nature Microbiology* ,

researchers at University of California San Diego School of Medicine have identified a class of microbial enzymes that drive ulcerative colitis, and have demonstrated a potential route for therapeutic intervention.

"Studies continue to show correlations between gut health and microbial constituents, but these trends don't exactly explain how the bacteria cause disease or what we can do about it," said study co-senior author David J. Gonzalez, Ph.D., associate professor of pharmacology at UC San Diego School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences. "This is the first study with experimental evidence that pinpoints a specific microbe driving ulcerative colitis, the protein class it expresses, and a promising solution."

Gonzalez and his collaborators are leaders in multi-omics—an approach that combines state-of-the-art genomics, proteomics, metabolomics and peptidomics to uncover the contents of a biological sample with unprecedented detail. The process of "digitizing" a sample allows the team to examine its biology at multiple scales and develop new hypotheses of disease progression.

"What makes UC San Diego special is our highly collaborative science, where world leaders in all the different 'omics' can come together to break new ground," said study co-senior author Rob Knight, Ph.D., professor and director of the Center for Microbiome Innovation at UC San Diego. "This study showcases the power of combining these technologies to explore biology in new ways."



Researchers hypothesize that ulcerative colitis may be triggered by bacterial proteases that damage the colonic epithelium and allow an influx of immune cells to drive further inflammation. Credit: University of California - San Diego

To study the gut microbiome, Gonzalez said the most useful biological sample is patient stool. It is also far less invasive to collect than more traditional blood or tissue samples.

"Once we had all the technology to digitize the stool, the question was, is this going to tell us what's happening in these patients? The answer turned out to be yes. We've shown that stool samples can be extremely informative in guiding our understanding of disease. Digitizing fecal material is the future."

The team found that roughly 40 percent of ulcerative colitis patients show an overabundance of proteases—enzymes that break down other proteins—originating from the gut resident Bacteroides vulgatus. They

then showed that transplanting high-protease feces from human patients into germ-free mice induced colitis in the animals. However, the colitis could be significantly reduced by treating the mice with protease inhibitors.

The team suggested that a stressor in the gut, such as nutrient deprivation, may increase protease production in an attempt to use proteins as an alternative nutrient source. However, these bacterial proteases may be damaging to the colonic epithelium or lining of the colon, allowing an influx of immune cells to then further exacerbate the disease.

Authors hope the study will inspire future work to confirm this hypothesis and develop protease-blocking drugs for use in humans. Now that a specific family of proteins has been implicated in this form of ulcerative colitis, they said, clinicians may also one day use antibody tests to quickly discern if a patient is a good candidate for protease treatment.

The researchers said their approach to stool analysis and multi-omic data integration might also be used to study other diseases, including diabetes, cancer, rheumatic and neurological conditions.

More information: Robert H. Mills et al, Multi-omics analyses of the ulcerative colitis gut microbiome link Bacteroides vulgatus proteases with disease severity, *Nature Microbiology* (2022). DOI: 10.1038/s41564-021-01050-3

Provided by University of California - San Diego