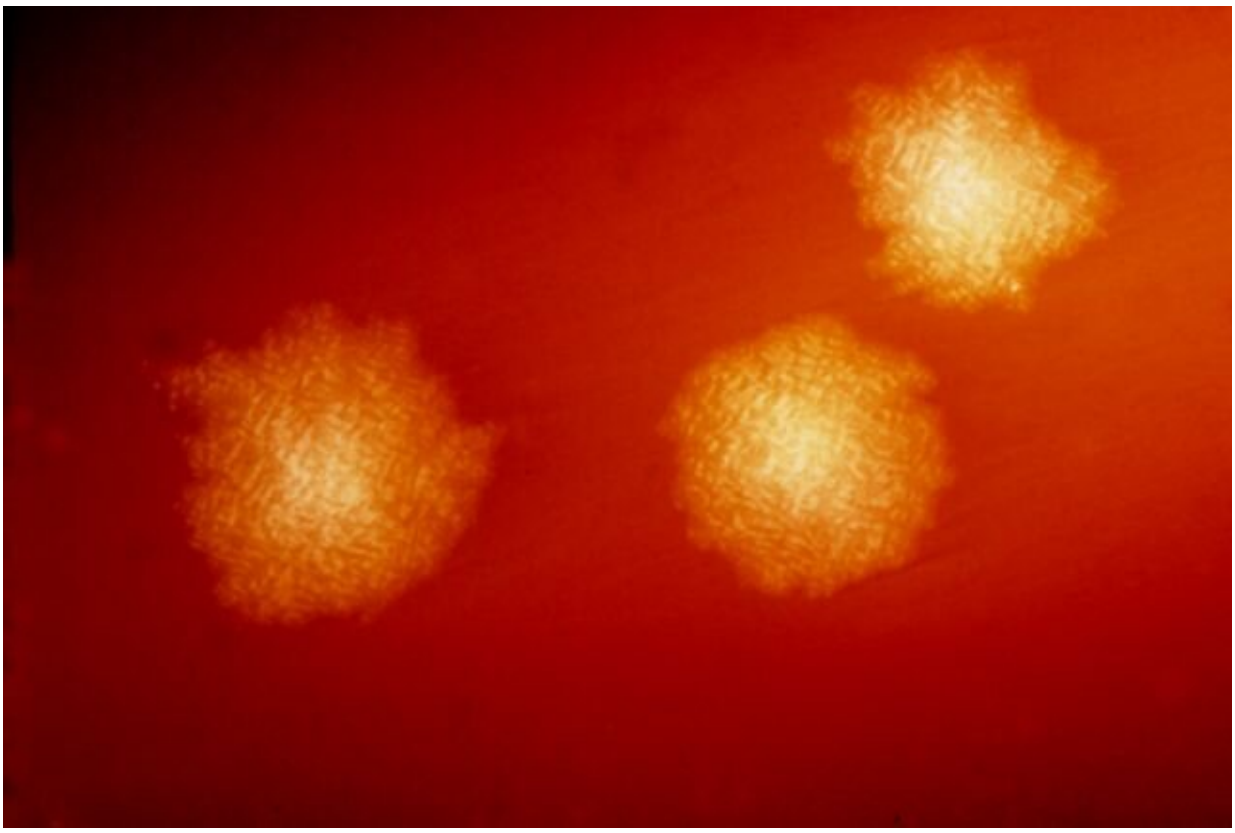
Researchers uncover metabolic secrets of anaerobes and identify new strategies to treat C. difficile infections

March 9 2023



This photograph depicts Clostridium difficile colonies after 48hrs growth on a blood agar plate; Magnified 4.8X. C. difficile, an anaerobic gram-positive rod, is the most frequently identified cause of antibiotic-associated diarrhea (AAD). It accounts for approximately 15–25% of all episodes of AAD. Credit: CDC

A team of investigators from Mass General Brigham's founding members, Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH), has identified metabolic strategies used by Clostridioides difficile to rapidly colonize the gut. The findings identify methods to better prevent and treat the most common cause of antibiotic-associated diarrhea and health care–acquired infections (HAIs). The team's approach has implications for understanding broader aspects of microbial metabolism, including responses to antibiotics, and production of important metabolites. Results are published in *Nature Chemical Biology*.

"Investigating real-time metabolism in microorganisms that only grow in environments lacking oxygen had been considered impossible," said co-corresponding author Lynn Bry, MD, Ph.D., director of the Massachusetts Host-Microbiome Center, associate medical director in Pathology at BWH, and an associate professor of Pathology at Harvard Medical School. "Here, we've shown it can be done to combat C. difficile infections—and with findings applicable to clinical medicine."

"C. difficile is the leading cause of hospital-acquired infections and a leading cause of antibiotic-associated diarrhea. Understanding its metabolic mechanisms at a cellular level may be useful for preventing and treating infections," said co–senior author Leo L. Cheng, Ph.D., an associate biophysicist in Pathology and Radiology at MGH and an associate professor of Radiology at Harvard Medical School.

C. difficile is an obligately anaerobic species of bacteria, which means it does not replicate in the presence of oxygen gas. C. difficile causes infections by releasing toxins that allow the pathogen to obtain nutrients from damaged gut tissues. Understanding how C. difficile metabolizes nutrients while colonizing the gut could inform new approaches to prevent and treat infections.

To complete their study, Bry and Cheng, faculty in the recently formed Mass General Brigham Pathology program, used a technology called high-resolution magic angle spinning nuclear magnetic resonance spectroscopy (HRMAS NMR) to study real-time metabolism in living cells under anaerobic conditions. The team incorporated computational predictions to detect metabolic shifts in C. difficile as nutrient availability decreased, and then developed an approach to simultaneously track carbon and nitrogen flow through anaerobe metabolism.

The researchers identified how C. difficile jump-starts its metabolism by fermenting amino acids before engaging pathways to ferment simple sugars such as glucose. They found that critical pathways converged on a metabolic integration point to produce the amino acid alanine to efficiently drive bacterial growth.

The study's findings identified new targets for small molecule drugs to counter C. difficile colonization and infection in the gut and provide a new approach to rapidly define microbial metabolism for other applications, including antibiotic development and the production of economically and therapeutically important metabolites.

More information: Leo Cheng, Elucidating dynamic anaerobe metabolism with HRMAS 13C NMR and genome-scale modeling, *Nature Chemical Biology* (2023). DOI: 10.1038/s41589-023-01275-9. www.nature.com/articles/s41589-023-01275-9

Provided by Mass General Brigham