Scientists shed light on microbial 'dark matter' with new approach

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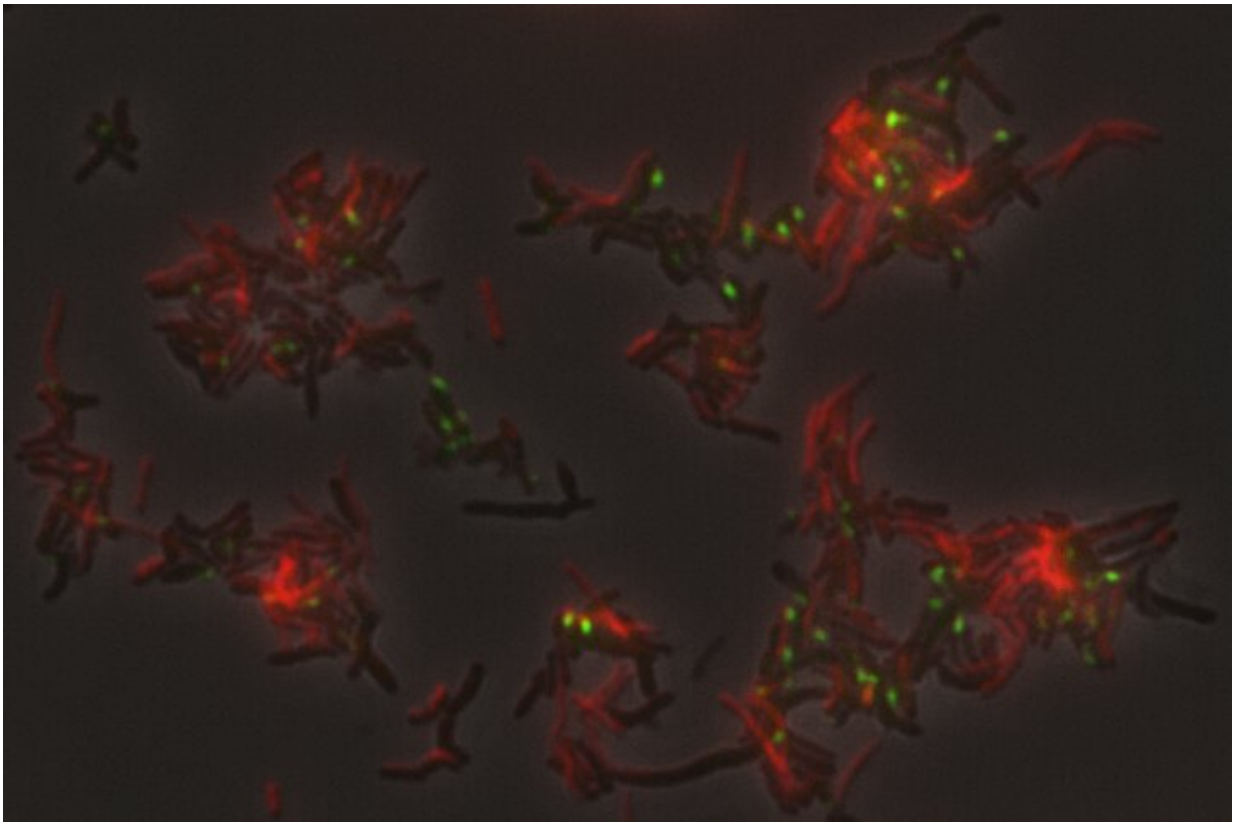

A co-culture of Actinobacteria-TM7, showing actinos in red and TM7 as the small green cells. Credit: Mircea Podar/Oak Ridge National Laboratory, U.S. Dept. of Energy

Scientists at the U.S. Department of Energy's Oak Ridge National Laboratory have demonstrated a way to isolate and grow targeted

bacteria using genomic data, making strides toward resolving the grand challenge of uncultivated microbial "dark matter" in which the vast majority of microorganisms remain unstudied in the laboratory.

Despite the importance of microorganisms to environmental and human health, only about half of the microbes within the human body have been grown in the lab for experimentation, while only a tiny fraction from most open environments have been cultured. Microbes can be extraordinarily difficult to grow simply because so little is known about them.

Over the past 20 years, scientists have made strides in understanding microbial life by sequencing the genome of microbes sampled in the field. However, extracting that genetic material kills the organism. In addition to inferring the characteristics of microbes from sequence data, scientists want to be able to study live organisms and prove theories about their form and function.

"One may think that we should be able to figure out what a microbe is and how to grow it just from the sequence data. But the problem is that we still don't know how to read a lot of that information. It's an enormous, multi-dimensional puzzle. You can make hypotheses, but until you can culture that organism you can only speculate at its physiology," said ORNL microbiologist Mircea Podar.

Podar and his team developed a method that relies on antibody engineering to identify and isolate specific microbes from complex human oral microbiome samples, as outlined in *Nature Biotechnology*.

The method leverages what scientists already know about predicting which proteins in a target microbe are typically located on a cell's membrane. Computational structure modeling was used to predict regions in those proteins that can serve as antigens. The scientists then

generated antibodies that naturally seek out and bind to those specific antigens. The scientists added a fluorescent tag to the antibodies that when illuminated, identified the target cells, which were then successfully isolated.

Mircea Podar is leading a team of ORNL scientists as they devise a new way to isolate and grow uncultured microbes for laboratory study. Credit: Genevieve Martin/Oak Ridge National Laboratory, U.S. Dept. of Energy

Reverse genomics method leads to success

The ORNL researchers did not have a natural source for the antigens since the microbes had not been previously grown. So they used

sequence data to help create the antigens—essentially reversing the order of how genomic information is typically used in microbiology, Podar explained.

In their experiments, the scientists first used genomic data from a group of human oral bacteria, TM7 or Saccharibacteria, previously associated with periodontal and inflammatory bowel disease. They successfully isolated three different species of TM7. In follow-up work, they also isolated a representative of a different uncultivated bacterial group, SR1, using the same strategy.

"It's been more than a decade since we began sequencing of uncultured microbes and found that while some are easy to grow, most are difficult. As a result, some scientists have become resigned to just relying on sequencing to analyze microbes," Podar said. "This is the first approach that lets us be selective as to which microbes we target, and it doesn't matter how few may be in the sample. It should be universally applicable to any microbial environment."

"We can answer fundamental questions about many uncultured microbes if we can culture them," Podar said. In his self-described work of "growing wild things," Podar has cultivated a Yellowstone microbe that grows symbiotically with another microbe in an acidic, near-boiling hot spring. His work has also contributed to the recent discovery of two genes that enable microbes to convert mercury into toxic methylmercury.

Cultivating knowledge of form and function

The next frontier is to expand cultivation on the many other lineages of life that we know about only from sequence data, Podar said. "Cultivation of multiple microbes at the same time is crucial. Then we can see who is interacting with whom, how they communicate with each

other and relate to each other as helpers or in competition, for instance. These are things we cannot get from sequencing, and it's one of the aspects we found about the TM7 in the oral microbiome."

Among the vital questions the scientists want to answer are how microbes sometimes form symbionts for survival, and why some thrive in certain conditions while others don't. "We want to understand how specific microbes evolved and what they may be doing for various microbiomes," Podar said. "We could apply that knowledge to human health, to how microbes benefit plants, and to microbes that could help us clean up contaminated areas."

More information: Targeted isolation and cultivation of uncultivated bacteria by reverse genomics, *Nature Biotechnology*, DOI: 10.1038/s41587-019-0260-6 , nature.com/articles/s41587-019-0260-6

Provided by Oak Ridge National Laboratory

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