Two DNA defense systems behind resilience of 7th cholera pandemic

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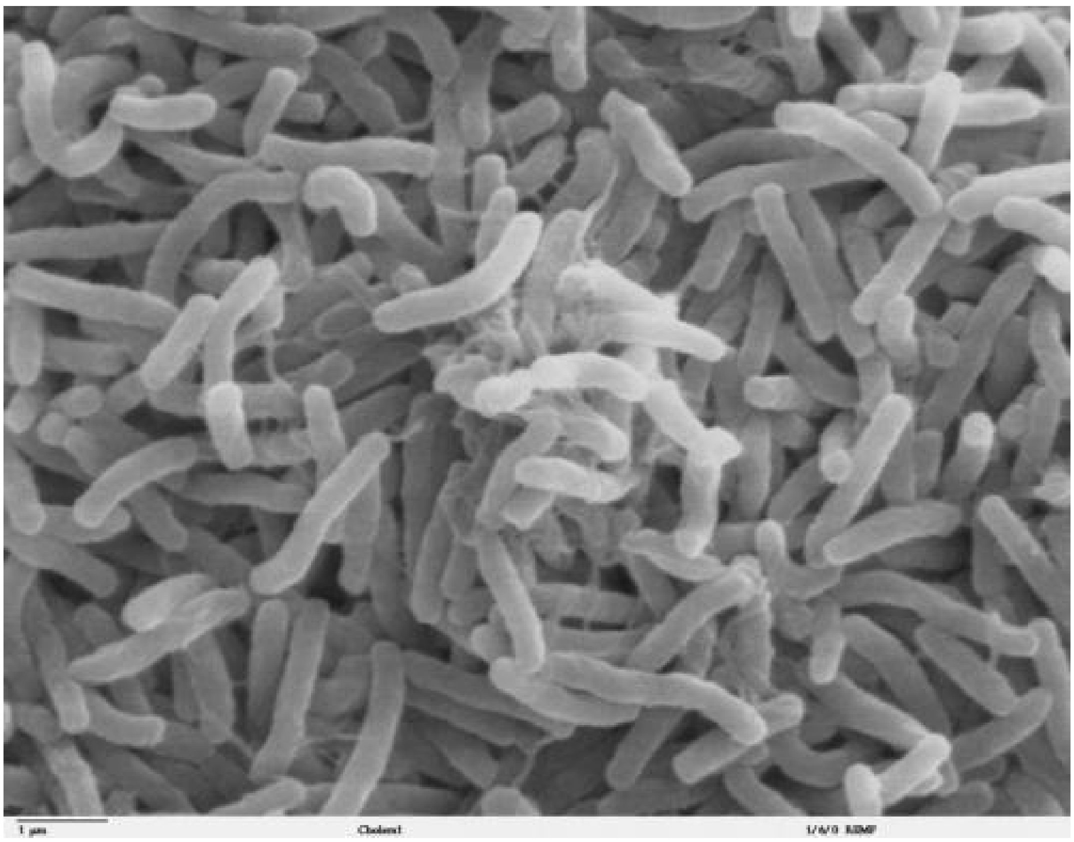

Scanning electron microscope image of Vibrio cholerae bacteria, which infect the digestive system. Credit: Ronald Taylor, Tom Kirn, Louisa Howard/Wikipedia

Cholera is caused by the bacterium Vibrio cholerae, a waterborne pathogen that infects the gut of humans through contaminated water and food. When ingested, V. cholerae colonizes the gut's inner surface, causing a watery diarrhea, that if left untreated, can lead to severe dehydration and death.

Cholera is still a problem, especially in less-developed or crisis-hit regions. The WHO reports that the ongoing seventh cholera pandemic is still responsible for up to four million infections, and up to 143,000 deaths each year.

Horizontal gene transfer

Only a few strains of V. cholerae can cause pandemic disease, with most being harmless aquatic organisms. This is because the pandemic strains have acquired specialized "toolboxes" of genes and other genetic elements called "pathogenicity islands", which can turn the bacterium into a pathogen.

Strains that cause cholera pandemics have acquired pathogenicity islands through a process known as "horizontal gene transfer", by which bacteria share genes both within and across species. Horizontal gene transfer is a powerful driver of bacterial evolution because it can quickly endow bacteria with new abilities that help them adapt and survive. But it is also indiscriminate, passing on genes that are unnecessary or even harmful to their new host.

Horizontal gene transfer often involves plasmids—self-replicating circular pieces of DNA found in bacteria that can carry up to hundreds of genes. But strains of V. cholerae that are causing the currently ongoing 7th pandemic of cholera only rarely carry plasmids while plasmids are abundant in related strains isolated from the environment instead of patients.

This surprising phenomenon caught the attention of scientists at EPFL, who decided to look into it. "We wanted to find out why plasmids are so rare in the 7th pandemic clade of V. cholerae, shedding light on how bacterial pathogens evolve," says Professor Melanie Blokesch who led the study with Milena Jaskólska and David W. Adams at EPFL's School of Life Sciences.

Two DNA defense systems

First, the researchers introduced a small model plasmid into V. cholerae strains from the 6th and 7th pandemics, as well as non-pandemic strains isolated from different water bodies. They then tracked the plasmid's stability over the course of many generations. Surprisingly, the model plasmid persisted in all strains, but was quickly eliminated from the 7th pandemic ones.

Encouraged, the scientists used genetic engineering methods to identify the parts of the V. cholerae genome responsible for this loss. This approach led to the discovery of two novel defense systems that work together to eliminate plasmids, and are encoded within two distinct pathogenicity islands.

Publishing in *Nature*, the researchers named the systems "DNA defense modules" (Ddm). The first one, DdmDE, is made up of two proteins that target and degrade small plasmids in a process helped by a second defense system, DdmABC.

This second system turned out to have a much broader role in bacterial defense. Not only can it enhance the elimination of small plasmids, but it can turn against the host cell, degrading its DNA and triggering a form of cell suicide. Essentially, DdmABC protects bacterial population against viruses by killing infected cells before the virus has time to replicate and spread.

The team also found that DdmABC targets large plasmids that often carry huge arrays of antibiotic-resistance genes, and can persist by jumping from one bacterium to the next, spreading multidrug resistance. "This finding might explain why the recent pandemic strains mainly carry antibiotic resistance integrated in their genome and not on plasmids," says Blokesch.

"The combined activity of these two defense systems solves the long-standing mystery of the missing plasmids in the 7th pandemic V. cholerae strains," say the researchers. "Furthermore, our discovery suggests that the ability of the 7th pandemic strains to defend against mobile genetic elements has likely played a key role in their evolution and success."

More information: Milena Jaskólska et al, Two defence systems eliminate plasmids from seventh pandemic Vibrio cholerae, *Nature* (2022). DOI: 10.1038/s41586-022-04546-y

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