Bacterial immune system boosts antibiotic effectiveness against cholera, study reveals

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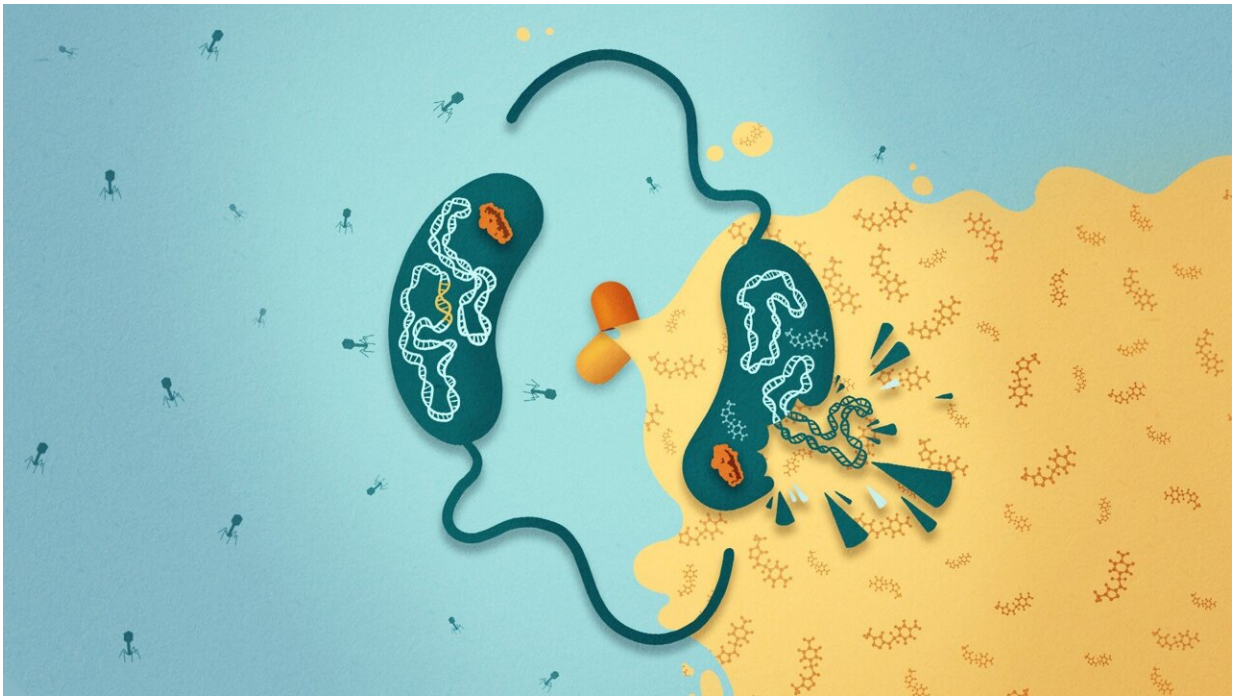

The bacterium Vibrio cholerae has a defense system against bacteriophages called CBASS. This phage defense mechanism makes the cholera pathogen sensitive to antibiotics. Credit: Lizah van der Aart / CMFI, University of Tübingen

Bacteria have an immune system that protects them against viruses known as bacteriophages. A research team from the Universities of Tübingen and Würzburg has now shown how this immune system

enhances the effect of specific antibiotics against the cholera pathogen Vibrio cholerae.

The immune system is the reason why this bacterium is particularly sensitive to one of the oldest known classes of antibiotics—the antifolates. The team's findings have been published in the latest issue of *Nature Microbiology*.

Vibrio cholerae causes severe cholera outbreaks worldwide and is endemic in many developing countries. Its immune system is made up of several molecular defense systems which protect the bacterium against attacks by various bacteriophages. One of these defense systems is called CBASS (cyclic-oligonucleotide-based antiphage signaling system). CBASS is activated when Vibrio cholerae is attacked by bacteriophages and causes the infected bacterium to destroy itself—thus preventing further infection of the bacterial population.

The research team led by Professor Dr. Ana Brochado has now shown that antifolate antibiotics activate the CBASS defense system even in the absence of bacteriophages. Thus, the activated CBASS potentiates the effect of the antibiotic and leads to the cell death of Vibrio cholerae. "As with an autoimmune disease, the bacterium is damaged by its own immune response," says Dr. Susanne Brenzinger, first author of the study.

Professor Dr. Ana Brochado's research team is investigating the effect of antibiotics using high-throughput screening—an automated method that tests the effect of thousands of substances on bacteria—in combination with computational analyses. This approach enabled the discovery of the interaction between CBASS and antibiotics.

"Antifolates were among the first antibiotics on the market; they inhibit the synthesis of folates, which are building blocks of DNA. Our results

show that more than 90 years after the introduction of antifolates, we still don't know everything about their mode of action. Surprisingly, the bacterial immune system modifies their effect," says Professor Brochado, who is researching systems biology of antibiotics in the Tübingen Cluster of Excellence Controlling Microbes to Fight Infections (CMFI).

Professor Brochado adds, "The more we know about the mode of action of antibiotics, the better we can use them. This will help us decide whether to use them alone, in combination with other antibiotics, or even in parallel with phage therapy—not only to treat cholera, but also against other bacterial infections. The appropriate and effective use of antibiotics is crucial to prevent further development of antibiotic resistance."

More information: Susanne Brenzinger et al, The Vibrio cholerae CBASS phage defence system modulates resistance and killing by antifolate antibiotics, *Nature Microbiology* (2024). DOI: 10.1038/s41564-023-01556-y

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