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Antibiotics: Major breakthrough to overcome bacterial resistance

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The resistance of a growing number of bacteria to current antibiotics represents one of the most serious threats to human health. The discovery of a new antibiotic active against these resistant bacteria could represent a real revolution in our fight against this scourge.

The introduction of antibiotics revolutionized medicine by providing effective treatment for many infectious diseases that were once fatal, as well as enabling major advances in surgery and organ transplantation.

Unfortunately, bacteria had not said their last word, because in recent decades we have witnessed the emergence of several strains that have developed resistance to some or more of these drugs, threatening to cancel out the progress made in the treatment of infections.

According to experts, this bacterial resistance to antibiotics is currently responsible for 5 million deaths each year worldwide and must be considered one of the main threats to public health in the 21st century (1).

DRY SOURCE

Bacteria are very abundant in the earth, with a density of 10 billion per gram of soil, and a diversity of several thousand species. These bacteria compete with each other by producing antibiotics to kill other species, according to the principles of Darwinian evolution.

Most of the antibiotics used in the clinic were discovered from laboratory cultures of bacteria that live abundantly in the soil, an approach that allowed the discovery of very effective antibiotics such as streptomycin, vancomycin, or tetracycline. However, this source has dried up over time and very few promising new antibiotics have emerged in recent decades.

This strategy based on the laboratory cultivation of bacteria has the disadvantage of ignoring the very large bacterial community that cannot be cultivated under standard laboratory conditions. However, these non-culturable bacteria account for more than 99% of existing bacterial species and therefore represent an untapped source of new generation bioactive molecules that can interfere with bacterial growth.

NEW MECHANISM OF ACTION

Recent advances suggest that the study of these non-culturable bacteria could considerably improve our arsenal of antibiotics for the treatment of infections. For example, this approach made it possible to isolate three molecules (teixobactin, lassomycin and amylobactin) with unique biochemical structures that block bacterial growth through novel mechanisms of action, much less likely to cause the emergence of resistant bacteria.

The merits of this approach have just been confirmed by the results of a recent study on a very rare environmental bacterium (Eleftheria terrae) (2). In this study, the researchers managed to obtain colonies of the bacteria after a very long incubation (12 weeks) in a specially adapted nutrient medium. The analysis of the molecules produced by these bacteria revealed the presence of a new molecule with unique characteristics, which they named clovibactin.

Tests conducted indicate that clovibactin has antibacterial activity against a wide range of Gram-positive pathogens, including resistant strains of S. aureus.

This antibiotic action is the result of a new mode of action, unknown until now, on three molecules essential for the synthesis of the walls which surround the bacteria and which are necessary for their survival.

The mechanism is very complex, but let us just say that clovibactin binds specifically to a molecule common to cell wall precursors (pyrophosphate), forming filaments on the surface that sequester these precursors and thus prevent the formation of the bacterial wall. The interest of this mechanism is that pyrophosphate is a metabolic intermediate that has no equivalent and therefore cannot be replaced.

The bacteria cannot therefore simply acquire a mutation that would allow it to circumvent the action of clovibactin, drastically reducing the possibility of developing resistance to this antibiotic.

These promising results suggest that the solution to the problem of antibiotic resistance is within our reach. Another example of human genius in finding in the nature that surrounds it the remedies for the ills that afflict it.

(1) Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022; 399: 629-655.
(2) Shukla R et al. An antibiotic from an uncultured bacterium binds to an immutable target. Cell 2023; 186: 4059-4073.