Genetic tradeoffs do not stop evolution of antibiotic resistance

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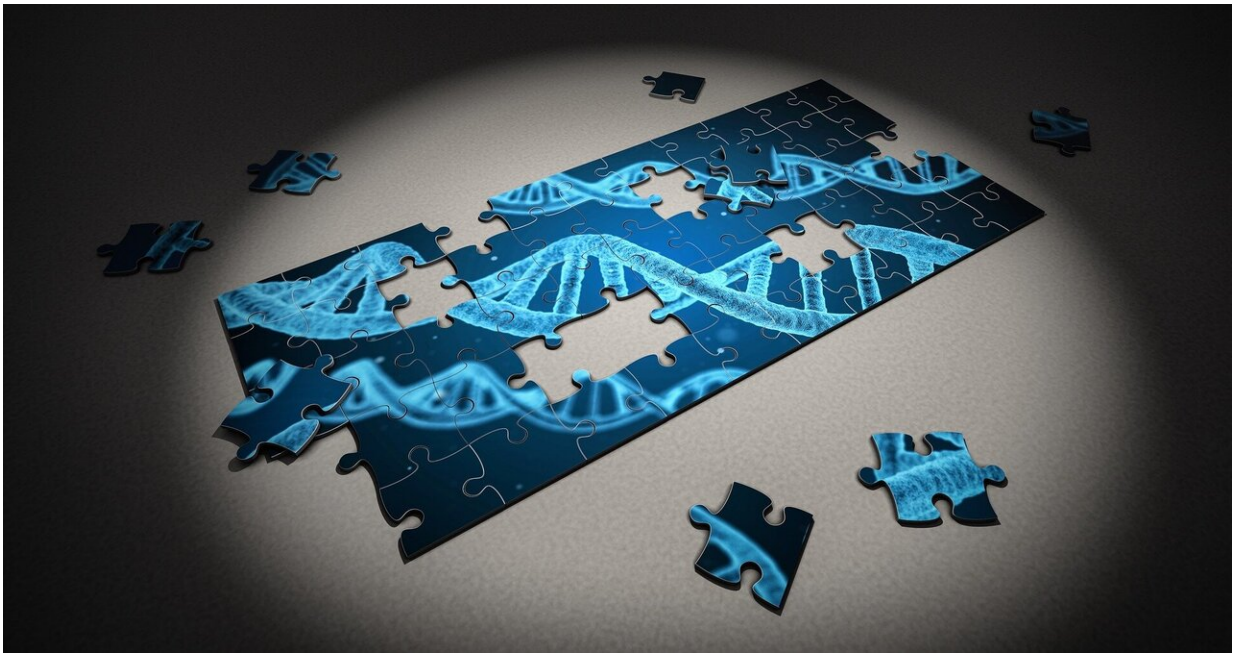

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Bacteria can still develop antibiotic resistance even in the face of challenging genetic tradeoffs, or compromises, associated with varying antibiotic concentrations, says a new study published today in *eLife*.

The rapid emergence of bacteria that are resistant to antibacterial drugs is a growing global health crisis. The findings provide valuable new

insights on how different concentrations of drugs affect the evolution of resistance in Escherichia coli (E. coli) bacteria, which can cause life-threatening blood infections.

Antibiotic resistance can emerge when a genetic mutation occurs in a single bacterium that allows it to survive the drug. While vulnerable bacteria die, the new resistant strain multiplies. It takes multiple mutations for bacteria to become highly resistant to antibiotics and each mutation likely comes with a few tradeoffs. For example, a mutation that allows bacteria to survive an antibiotic may slow the organism's growth when no antibiotic is present. The more tradeoffs there are on the evolutionary path to drug resistance, the harder it should be for resistance to emerge.

"If the fitness landscape is smooth with few tradeoffs, the evolving bacterial population can easily become resistant, whereas in a rugged landscape with lots of tradeoffs one expects it to get stuck at suboptimal peaks and to be less likely to become resistant," explains lead author Suman Das, Research Associate at the Institute for Biological Physics, University of Cologne, Germany.

To learn more about how different antibiotic concentrations affect the evolution of resistance in E. coli, Das teamed up with Susana Direito, Bartlomiej Waclaw and Rosalind Allen at the University of Edinburgh, UK, who exposed the bacteria to different concentrations of the antibiotic ciprofloxacin. They tracked the growth rate of bacteria in these circumstances and the tradeoffs that occurred, and Das created a mathematical model based on their data.

The model showed that the paths to resistance become more difficult to traverse in the presence of tradeoffs. But, contrary to the researchers' expectation, the obstacles created by the tradeoffs did not make the emergence of resistance less likely.

"The evolution of resistance wasn't constrained by fitness landscape ruggedness," Das says. "At the same time, as more tradeoffs emerged, it became more difficult for us to predict the evolutionary path the bacteria would take towards resistance."

Their model did suggest, however, that bacteria may reverse course and regain susceptibility to antibiotics when faced with lower concentrations of the drugs.

"Our model provides a principled framework for addressing the evolution of antibiotic resistance in clinical and environmental settings, where drug concentrations vary widely," adds senior author Joachim Krug, Group Leader at the Institute for Biological Physics, University of Cologne. "It could one day be used to help scientists design new drugs or treatment protocols that prevent or slow the emergence of antibiotic resistance."

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