Scientists uncover surprising twist in the ways bacteria spread antibiotic-resistant genes

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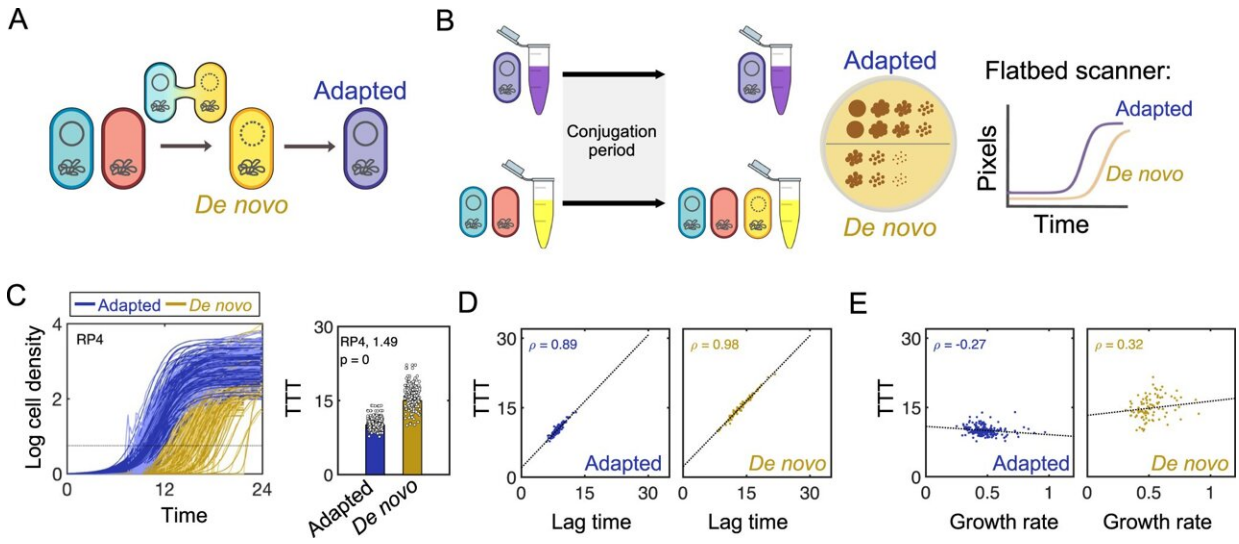

Quantifying plasmid acquisition costs with single-colony resolution. A Schematic illustration of conjugation between a donor (blue) and recipient (red) cell, generating a de novo transconjugant (yellow). Over time, the de novo transconjugant adapts to the plasmid, becoming an adapted transconjugant (purple). B Schematic illustration of the acquisition cost protocol. C Left: Log cell density in pixels (y-axis) of RP4 de novo (yellow, n = 96) and adapted (purple, n = 208) transconjugants over time (x-axis, hours). The black horizontal line indicates the time-to-threshold (TTT) in hours. Right: TTT (y-axis) of de novo (yellow) compared to adapted (purple) transconjugants. Markers correspond to the TTT of individual colonies pooled across seven independent biological replicates. Bar height represents the mean TTT of all colonies. The acquisition cost (1.49) is determined to be statistically significant using a two-

sided t-test (p value shown) between the TTT of adapted and de novo populations. D, E Individual de novo (yellow, right) and adapted (purple, left) colony lag times (D) or growth rates (E) (x-axis) plotted against their corresponding TTT (y-axis). In all cases, TTT is defined as the time in hours it takes the bacterial population to reach a 'threshold' density within the exponential phase; the threshold used here is 0.8. Where applicable, the Pearson correlation coefficient is reported (ρ) and the linear regression line of best fit is shown in black. All figure data uses recipient strain RB933. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-38022-6

Scientists have found a counterintuitive wrinkle in the way bacteria spread antibiotic-resistant genes through small circular pieces of DNA called plasmids.

Plasmids, found in bacteria and some other microorganisms, are physically separate from chromosomal DNA and can replicate on their own. Bacteria can acquire plasmids from other bacterial cells or from viruses, and as plasmids build up, they give bacteria antibiotic resistance.

But some plasmids are easier for bacteria to acquire than others. What makes these plasmids spread more easily?

While common sense might suggest that plasmids that spread the easiest are the ones that allow bacteria to grow the fastest, a new study in *Nature Communications*, led by Allison Lopatkin, an assistant professor of chemical engineering at the University of Rochester, outlines the surprising evolutionary tradeoff between lag time and growth rate.

Fast acquisition of plasmids comes at a cost

"You would think that something that's able to grow faster will always do better, but we found that's not true because the acquisition costs manifest

in a delay rather than a growth rate," says Lopatkin. "Taking a little bit longer to let that plasmid become established ultimately helped the gene spread faster."

Lopatkin and her team studied the growth rates of single colonies of bacteria immediately following plasmid acquisition. Across nearly 60 conditions covering diverse plasmids, selection environments, and clinical strains, they found that intermediate-cost plasmids outcompete both their low and high-cost counterparts.

The research shows plasmid costs are more complex than previously believed and is a step toward better understanding why certain types of pathogens are better at acquiring plasmids than others. If scientists can understand what controls the costs of acquiring a plasmid, they can potentially use that information to limit the spread of antibiotic-resistant genes.

"We see horizontal gene transfer as an engineering tool to control how genes can spread and help bacterial communities interact," says Lopatkin. "By understanding the individual parts, we hope not only to be able to fight things like antibiotic resistance, but also to use plasmids to deliver genes that can help natural bacteria degrade oil from oil spills. There are many applications microbiomes can be useful for."

Lopatkin and her lab plan to further investigate the underlying genetic and environmental conditions that successfully lead to horizontal gene transfer. Lopatkin's team will use computational modeling, bioinformatics, and mechanistic experiments to study the molecular factors favoring the formation of new strain-plasmid combinations.

"Ultimately, we hope to be able to predict high-risk gene transfer before it occurs, thereby allowing us to explore novel control and treatment strategies," says Lopatkin.

More information: Mehrose Ahmad et al, Tradeoff between lag time and growth rate drives the plasmid acquisition cost, *Nature Communications* (2023). DOI: 10.1038/s41467-023-38022-6