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Sulfonamide antibiotic rescues bacteria from phage-induced collapse

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Phage-antibiotic combinations are a promising strategy to combat antimicrobial-resistant pathogens, but we currently lack mechanistic understanding of underlying bacterial responses. Here, we characterize the interaction between the antifolate antibiotic sulfamethoxazole and phage T4 in *Escherichia coli*.

We combine quantitative with molecular and phage biology approaches, namely checkerboard assays, time-lapse microscopy and one-step growth curves, to characterize phage-sulfamethoxazole interactions in *E. coli*.

Sulfamethoxazole protects bacterial cultures from rapid T4-induced collapse, even at subinhibitory concentrations. Checkerboard assays show similar effects with phage T2, but not phages T5 or T7. Preliminary single-cell time-lapse microscopy shows delayed cell lysis, suggesting slower propagation of infective progeny, which was confirmed by time-resolved phage titer assays. After introducing the sulfamethoxazole resistance gene *sul2* into *E. coli*, the protection of the drug is completely abolished indicating that the on-target antifolate effect is driving the suppression of T4-induced collapse.

Our results identify a previously uncharacterized antagonistic interaction between sulfamethoxazole and T4, showing how this antibiotic can impact phage replication, even at subinhibitory concentrations. Ongoing experiments include a large genetic screen and dual-transcriptomics and quantitative proteomics to identify host factors underlying the molecular mechanism of this interaction.

Reference #1

Theuretzbacher U et al (2020): The global preclinical antibacterial pipeline. Nat Rev Microbiol // 10.1038

Reference #2

Fungo G et al (2023): “Two Is Better Than One”: The Multifactorial Nature of Phage-Antibiotic Combinatoria

Reference #3

Brochado AR et al (2018): Species-specific activity of antibacterial drug combinations. Nature // 10.1038/

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