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Dozens of phage proteins block retron defense by targeting its toxicity on the ribosome

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Retron-Sen2 from S. Typhimurium encodes a tripartite toxin-antitoxin (TA) system that defends bacteria against phage via abortive infection. Its toxic effector, RcaT, is a predicted ribosyltransferase neutralized by the msDNA-reverse transcriptase complex, with msDNA acting as a sensor for infection. RcaT retrons represent the most prevalent retron family, and other families likely share similar architecture and activation principles. Yet despite growing understanding of retron families generally, RcaT's mode of action, and more broadly how phages circumvent retrons, remains unclear.

To explore the diversity of phage-encoded anti-defense mechanisms, we used metagenomic phage DNA libraries and a forward genetics screen to identify proteins blocking RcaT toxicity. We found over 50 distinct proteins, most lacking obvious homology to known proteins. Many inhibit divergent RcaT homologues and frequently occur as blocks within phage genomes.

To understand how these blockers function, we first resolved RcaT's mechanism: it arrests translation termination by ADP-ribosylating conserved histidines on release factors (RF) 1 and 2, inactivating them and causing ribosome stalling and collisions at the termination codon. Some phage blockers mimic host proteins involved in this toxicity (such as RFs and ribosomal protein L7, RcaT's binding target) while others reverse ADP-ribosylation. However, most blockers act through unidentified mechanisms, and many bind the ribosome directly. This suggests phages preferentially target the conserved component of the toxicity mechanism (the ribosome) rather than the effector itself: a strategy that could let small phage genomes counter hundreds of bacterial defense systems, enabling broadly acting anti-defenses and convergent evolution in the phage-bacteria arms race.

Reference #1

Reference #2

Reference #3

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