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2025 SEA Symposium Abstract

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Unveiling Toxic Phage Genes: Genome-Wide Overexpression Screen of Bacteriophage Jeeves Reveals Insights into Phage-Host Dynamics

Bacteriophage Jeeves, a temperate siphoviridae in cluster A14, has a genome of 52,466 base pairs encoding 102 genes, including one tRNA. To explore the functional roles of these genes, we conducted a genome-wide overexpression screen to assess their impact on the growth of *Mycobacterium smegmatis*. The screen identified 56 protein-coding genes with varying levels of toxicity: 23 genes reduced colony size, 21 exhibited moderate cytotoxicity, and 12 were highly toxic, completely halting host growth upon overexpression. Functional analysis revealed that 32 (57%) of the toxic genes are of unknown function, highlighting the potential for discovering novel mechanisms of phage-host interactions. Among the characterized toxic genes, seven encode proteins involved in DNA replication, three are linked to transcription, ten are associated with virion structure, and two regulate bacterial lysis. These results emphasize the diverse roles of phage-encoded proteins in both inhibiting host growth and regulating the phage lifecycle. This study underscores the utility of genome-wide overexpression screens for identifying toxic phage genes and uncovering their functional roles. The high proportion of uncharacterized toxic genes presents an exciting opportunity to expand our understanding of phage biology and host-phage dynamics. By integrating experimental data with bioinformatics tools, this research contributes to advancing bacteriophage genomics and exploring their potential applications in biotechnology and antimicrobial therapy.