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Hidden Functional Diversity among Type V-A CRISPR Effectors

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Bacterial antiphage defenses, including CRISPR-Cas, are commonly classified according to their evolutionary relationships, presence of known functional domains, or genomic neighborhood. Yet, as viral predation drives rapid diversification, incomplete sequence sampling and fragmented knowledge of bacterial immunity often undermine our ability to reliably predict defense functions. For example, we have recently uncovered functional variation hidden among well-known type V-A CRISPR-Cas effectors. Unlike DNA-targeting Cas12a, these additional Cas12a2 and Cas12a3 clades target RNA. Further yet, their downstream nuclease activities and physiological outcomes differ strikingly. Activated Cas12a2 indiscriminately degrades ssRNA, ssDNA, and dsDNA. In bacteria, collateral DNA damage triggers an SOS response and growth arrest, preventing phage dissemination. We harnessed this property to selectively eliminate eukaryotic cells based on viral transcripts or oncogenic mutations. Cas12a3 instead recruits tRNAs through a novel loading domain and cleaves their conserved 3′-CCA tails. The resulting tRNA truncation arrests growth and limits phage replication. By designing synthetic reporters that mimic tRNAs, we expanded the multiplexing capacity of existing CRISPR-based diagnostic platforms for viral RNA detection. Together, these effectors show how evolutionary remodeling of a shared effector scaffold can redirect immunity from broad nucleic acid destruction to selective inactivation of the translation machinery, underscoring both the limits of predicting molecular function and persistent gaps in our knowledge of bacterial defenses. Looking ahead, we aim to systematically explore bacterial immunity across the evolutionary landscape to determine how variation in activation, regulation, molecular mechanism, and physiological outcome generates distinct antiviral strategies and new opportunities for biotechnology

Reference #1

Reference #2

Reference #3

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