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Poster #65: Fun/Z is an abortive immunity system related to archaeal and eukaryotic replication component

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Temperate bacteriophages can benefit by protecting their hosts against other phages. The P2-like group of phages encodes a diversity of compact immunity modules. We reveal that the Fun/Z defense system of prophage P2 is related to ORC/Cdc6 domains involved in archaeal and eukaryotic DNA replication. In contrast to related STAND immunity ATPases, Fun/Z lacks predicted sensor or effector domains yet provides abortive defense. In vitro, Fun/Z exhibits DNA binding activity with specificity for ssDNA.

ORC proteins are single-turnover ATPases, and ATP binding activates the protein to promote DNA recognition. Interestingly, Fun/Z contains a modified Walker B motif ("DG"), implying slow ATP hydrolysis. Mutations in Walker A or B abolish defense, whereas restoring the canonical "DE"motif or introducing an ATP-trap ("DQ") mutation—expected to stabilize an activated conformation—makes Fun/Z expression highly toxic. Metabolic labeling revealed that these toxic mutants inhibit DNA replication. Together with its DNA-binding activity and homology to ORC proteins, this suggests that Fun/Z activation could interfere with replication initiation.

A search for Fun/Z escapers identified Vequintavirinae phage Msk10 with genome duplications. Analysis of the duplicated region uncovered Fzad (Fun/Z anti-defense) as the first characterized Fun/Z inhibitor, highlighting the importance of gene dosage effects in anti-defense mechanisms.

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Reference #1

Reference #2

Reference #3

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