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Deoxydinucleotides activate the bacterial anti-phage defense system ApeA

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Bacteria carry many antiviral defense systems, most of which rely on toxic effectors that must stay inactive until infection. How infection is actually sensed is still unknown for most of them. Here we focus on ApeA, a single-protein system with a HEPN RNase domain. Testing six homologs against a large E. coli phage panel revealed distinct, homolog-specific protection profiles. Protection fails at high MOI, suggesting abortive infection, and RNA-seq of infected cells showed ApeA cutting host tRNAs inside the anticodon loop –the cell shuts down its own translation to strand the phage.

Cryo-EM of five homologs revealed unexpectedly large doughnut-shaped decamers, with HEPN active sites lining a tRNA-sized central channel and a conserved pocket sitting far from the catalytic center. In Ec2ApeA that pocket holds a 5′-phosphorylated deoxydinucleotide ending in guanosine (pdNG). Mutating the pocket or the oligomerization interface abolishes defense, and a specific loop shifts upon ligand binding, apparently relaying the signal across the ring. Deoxydinucleotides trigger tRNA cleavage in vitro; depleting them in cells shuts down ApeA toxicity.

We propose Ec2ApeA is sensing debris of its own genome, chewed up by phage nucleases –a new class of immune activator.

Reference #1

Reference #2

Reference #3

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