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Metabolic reconstitution in the NAD+ battlefield: phages and bacteria in a molecular arms race

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Bacteria defend against phage infection through a variety of antiphage defense systems. Many of these systems deplete cellular NAD+ in response to infection by cleaving it into nicotinamide and ADP-ribose or related metabolites. We previously showed that a substantial fraction of phages encode the NAD+ reconstitution pathway 1 (NARP1), which restores NAD+ from its degradation products and counteracts NAD-depleting immunity.

Recently, we described the next stage of this metabolic arms race. We show that the aRES family of antiphage defense systems degrades NAD+ into nicotinamide and ADPR-1″-phosphate, a product that cannot be recycled by canonical NARP1. In response, phages have evolved an expanded NAD+ reconstitution pathway, NARP1-AP, which encodes a phosphatase that converts ADPR-1″-phosphate into ADP-ribose, thereby restoring NAD+ biosynthesis and overcoming aRES-mediated defense.

Our findings demonstrate how reciprocal innovation in NAD metabolism drives the co-evolution of bacterial defense and phage counterdefense, illustrating metabolic reconstitution as a powerful strategy in the phage–bacteria arms race.

Reference #1

Osterman, I. et al. Phages reconstitute NAD+ to counter bacterial immunity. Nature 634, 1160–1167 (2024).

Reference #2

Osterman, I. et al. Bacterial defense via RES-mediated NAD+ depletion is countered by phage phosphatases.

Reference #3

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