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Poster #70: Exploring potential mechanisms of programmed cell death in Legionella phage defense: Interplay of NAD(H) depletion and the effector phospholipase PlaB

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Legionella pneumophila, an intracellular pathogen of human lungs and environmental protozoa, possesses a diverse array of virulence factors shaped by its niche. One such factor, the highly active phospholipase A PlaB, localizes to the bacterial outer membrane and contributes to virulence in host cells. Here, we propose an additional function for PlaB as an intrinsic cell death effector involved in phage defense.

Our findings reveal an intriguing regulatory mechanism in which intracellular NAD(H) controls PlaB activity. At physiological NAD(H) levels, inactive PlaB tetramers are stabilized by NAD(H) binding. Upon NAD(H) depletion, PlaB dissociates into active dimers, unleashing potent phospholipase activity. We hypothesize that activated PlaB targets bacterial membranes from within the cytosol, triggering autolysis and thereby limiting phage replication through an abortive infection strategy.

Consistent with NAD(H) being central for regulation of PlaB‘s activity, gene co-occurrence analyses show that PlaB can be found with genes encoding NAD(H)-consuming enzymes, such as RES-Xre toxin-antitoxin systems and SIR2- and TIR-domain proteins, suggesting a coordinated regulatory network. Supporting this observation, co-expression of PlaB with such enzymes in *E. coli* and *L. pneumophila* leads to rapid, PlaB-dependent cell death under low NAD(H) conditions.

These findings support a model in which NAD(H) serves as a molecular switch controlling PlaB activity and identify PlaB as a candidate effector linking NAD(H) depletion to altruistic cell death and abortive infection mechanism during possible phage infection. This work expands the functional repertoire of PlaB beyond virulence and suggests a possible implication in phage defense in *L. pneumophila*.

Reference #1

Diwo M, Michel W, Aurass P, Kuhle-Keindorf K, Pippel J, Krausze J, Wamp S, Lang C, Blankenfeldt W, Fliege

Reference #2

Kuhle K, Krausze J, Curth U, Rössle M, Heuner K, Lang C, Flieger A. Oligomerization inhibits Legionella pn

Reference #3

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