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Poster #28: Domain swapping reveals deep conservation of death-domain immune signaling

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Death domains are central scaffolds of innate immune signaling in animals, where upon pathogen recognition they rapidly nucleate higher-order signalosomes that control inflammatory responses and programmed cell death. Homologous domains were recently identified in putative bacterial defense systems, where they occur in combination with diverse cell death effectors in a mix-and-match architecture. However, whether death domains share conserved mechanisms of assembly, signaling, and immune response execution across the tree of life remains unknown. We expressed several putative bacterial systems containing death domain homologues in E. coli and conducted infection assays. Our results show that these bacterial systems confer immunity against phage infection. Remarkably, anti-phage immunity remains functional in bacteria when bacterial and mammalian death-domain homologues are exchanged in chimeric constructs. Structure-guided mutagenesis demonstrated that residues conserved in bacterial and mammalian death domains, together with conserved effector active-site residues, are essential for immune function. These findings support a highly conserved mechanism of death-domain-mediated immune signaling that predates the emergence of eukaryotes. Our work therefore establishes bacterial death-domain systems as tractable models for discovering novel bacterial immune mechanisms and investigating the evolutionary conservation of supramolecular immune signaling across the tree of life.

Reference #1

Reference #2

Reference #3

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