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Processing of forked DNA activates a helicase-nuclease immune system

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Innate immune systems detect molecular signatures of infection to initiate antiviral defence, yet the identity of pathogen-associated signals that distinguish phage from host nucleic acids remains incompletely understood. While recent work has shown that nucleic acid structures can act as triggers for bacterial defense systems, how these structural signals are coupled with immune activation remain unclear. Here we show that forked DNA structures activate a helicase-nuclease immune complex in type III Druantia through a processing-dependent mechanism. Using cryo-electron microscopy and biochemical reconstitution, we find that the exonuclease DruH processes 3′ DNA termini to generate 5′ overhangs that recruit and activate the helicase-nuclease DruE at duplex-single-stranded DNA junctions. Structural analysis of the DruE-DruH complex reveals how substrate-dependent assembly remodels an autoinhibited helicase dimer into an active DNA degradation complex. Functional assays demonstrate that coordinated nuclease and helicase activities enable efficient degradation of forked DNA substrates and mediate phage defense without detectable host toxicity. Together, our findings define a mechanism in which enzymatic processing of replication-associated DNA structures licenses immune activation, providing a framework for how nucleic acid architecture is coupled to effector activation in bacterial immunity.

Reference #1

Reference #2

Reference #3

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