Molecular mimicry to exploit the host-cell ubiquitination pathway

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Ubiquitination of target proteins is mediated by the sequential action of three types of enzyme: Ub–activating enzymes (E1s), Ub–conjugating enzymes (E2s), and Ub ligases (E3s). Legionella pneumophila, the causative agent of Legionnaire's disease, exploits the host ubiquitination machinery by producing its own E3 ligase mimics, which hijack the E2–Ub complex to target different host proteins for ubiquitination and subsequent degradation. Legionella pneumophila encodes its own molecular mimics of E3 ligases, including the effector protein RavN, thereby subverting the ubiquitin pathway for its own benefit during infection. Using protein crystallography, we have revealed that the fold of RavN shows only residual resemblance to conventional eukaryotic E3s. The N-terminal region of RavN displays a U-box-like motif that lacks the central alpha helix commonly found in other U-box domains, indicating that RavN is an E3 ligase relic that has undergone significant evolutionary alteration. Yet its mode of interaction with E2 enzymes, host proteins that are important for the ubiquitin transfer reaction, has been preserved throughout evolution, and substitution of amino acid residues within the predicted E2 binding interface render RavN inactive.