The *Shigella flexneri* effector IpaH1.4 degrades the E3 ligase RNF213 and protects *Shigella* against ubiquitylation

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Ubiquitylation is a conserved pathway that is required for the detection and subsequent clearance of infectious bacteria, viruses, and fungi. Given that ubiquitylation is a clear threat to cytosolic pathogens, cytosolic bacteria like *Burkholderia* are resistant to ubiquitylation. We therefore asked whether the professional cytosolic pathogen and causing agent of bacillary dysentery, *Shigella flexneri* could also escape cytosolic ubiquitylation. By using bacterial genetics and cell biology approaches, we uncovered for the first time how *Shigella* counteracts the host ubiquitylation machinery. Mechanistically, we found that *Shigella* secretes the virulence factor IpaH1.4 which triggers the proteasomal degradation of RNF213, an E3 ligase responsible for ubiquitylating multiple pathogens. Indeed, *S. flexneri* mutants lacking IpaH1.4 are coated with ubiquitin and RNF213 in the host cytosol. We also discovered that the conjugation of linear and lysine-linked ubiquitin to bacteria is solely dependent on RNF213 and independent of the E3 ligase LUBAC. Strikingly, we found that ubiquitylation of *S. flexneri* is insufficient to restrict *S.flexneri*. This finding suggests that *S. flexneri* uses additional virulence factors to escape from host defenses that operate downstream from RNF213-driven ubiquitylation. As a whole, we have discovered the first direct inhibitor of RNF213-driven immunity against *S.flexneri.*

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