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Characterization of a Putative Type 1 Toxin-Antitoxin System in Shigella Flexneri

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Abstract : Shigella is a pathogenic bacterium responsible for shigellosis, a severe diarrheal disease that claims the lives of immunocompromised individuals worldwide. To develop therapeutics against this disease, an understanding of the molecular mechanisms underlying the pathogen's physiology is crucial. Small non-coding RNAs (sRNAs) have emerged as important regulators of bacterial physiology, including as components of toxin-antitoxin systems. In this study, we investigated the role of RyfA in S. flexneri physiology and virulence. RyfA, originally identified as an sRNA in Escherichia coli, is conserved within the Enterobacteriaceae family, including Shigella. Whereas two copies of ryfA are present in S. dysenteriae, all other Shigella species contain only one copy of the gene. Additionally, we identified a putative open reading frame within the RyfA transcript, suggesting that it may be a dual-functioning gene encoding a small protein in addition to its sRNA function. To study ryfA in vitro, we cloned the gene into an inducible plasmid and observed the effect on bacterial growth. Here, we report that RyfA production inhibits the growth of S. flexneri, and this inhibition is dependent on the contained open reading frame. In-silico analyses have revealed the presence of two divergently transcribed sRNAs, RyfB1 and RyfB2, which share nucleotide complementarity with RyfA and thus are predicted to function as anti-toxins. Our data demonstrate that RyfB2 has a stronger antitoxin effect than RyfB1. This regulatory pattern suggests a novel form of a toxin-antitoxin system in which the activity of a single toxin is inhibited to varying degrees by two sRNA antitoxins. Studies are ongoing to investigate the regulatory mechanism(s) of the antitoxin genes, as well as the downstream targets and mechanism of growth inhibition by the RyfA toxin. This study offers distinct insights into the regulatory mechanisms underlying Shigella physiology and may inform the development of new anti-Shigella therapeutics.

Keywords : sRNA, shigella, toxin-antitoxin, Type 1 toxin antitoxin
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