The Effects of Nitazoxanide on Bacterial Virulence Factor Assembly by the Chaperone/Usher Pathway

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Antibiotic misuse has caused bacteria to evolve resistance, raising the potential for widespread, devastating health crises. Novel therapeutic alternatives to antibiotics seek to target virulence factors, which facilitate bacterial pathogenesis and are secreted by outer membrane complexes. The chaperone/usher (CU) pathway is a conserved assembly and secretion system in Gram-negative bacteria that is responsible for the biogenesis of many virulence factors. The anti-parasitic small molecule nitazoxanide (NTZ), has been shown to decrease surface expression of several CU assembled pili in E. coli, suggesting its action against the pathway. In a previous study, it was shown that NTZ also caused a dose-dependent decrease in surface expression of the fraction 1 (F1) capsule, a CU virulence factor utilized for host immunoevasion in Yersinia pestis, the causative agent of bubonic plague. The purpose of this study was to determine how NTZ inhibits the formation of the F1 capsule by examining the drug's effects in different stages of F1 capsule biogenesis. Through analysis of periplasm and outer membrane (OM) fractions of treated bacteria, it was discerned that NTZ's inhibitory effects are due to fewer OM usher molecules, rather than fewer F1 capsule subunits being produced by the bacteria. These findings demonstrate that NTZ has a unique mechanism of action against CU assembled virulence factors, as it inhibits the expression of virulence factors and does not interfere with vital processes of the cell. NTZ likely targets a common biogenesis requirement in Gram-negative bacteria, which when identified may lead to the development of a novel class of therapeutics to circumvent the development of antibiotic resistance.

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