The Effects of Nitazoxanide on Chaperone/Usher Pathway Assembled Virulence Factors in Gram-Negative Bacteria

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Antibiotic misuse has caused bacteria to evolve resistance, raising the potential for devastating health crises. To combat antibiotic resistance, novel therapeutic alternatives seek to target virulence factors, which facilitate bacterial pathogenesis and are secreted by outer membrane complexes. The chaperone/usher (CU) pathway is an assembly and secretion system that is responsible for the biogenesis of many virulence factors in Gram-negative bacteria. The anti-parasitic drug, nitazoxanide (NTZ), has been shown to decrease surface expression of several CU pathway assembled pili in E. coli. The purpose of this study was to determine if NTZ inhibited the formation of the Fraction 1 (F1) capsule, a virulence factor utilized for immunoevasion by Yersinia pestis. To analyze capsule formation in the presence of NTZ, mutated E. coli plasmids containing the Caf1A usher were administered varying concentrations of NTZ and tested against plasmids lacking the usher. Cultures of these plasmids were grown at 37°C to induce capsule expression, and the capsule protein surface-assembled was extracted and analyzed by gel electrophoresis. When surface protein levels were analyzed, experimental groups containing the Caf1A usher plasmid exhibited a dose-dependent decrease in capsule levels, while those without the usher lacked the F1 capsule. These results suggest that the CU complex is a viable target for novel therapeutics, and that NTZ inhibits the functionality of a vast array of CU systems. Further research into NTZ's interaction with CU systems may pinpoint a common biogenesis requirement targeted by NTZ, optimizing a novel class of therapeutics to circumvent antibiotic resistance in Gram-negative pathogens.

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Third Award of $1,000