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Dam* methylation has profound effect on antibiotic resistance in uropathogenic *Escherichia coli

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Urinary tract infections (UTIs) are primarily caused by uropathogenic *Escherichia coli* (UPEC) bacteria and result in high morbidity and high economic costs. Because many of these bacteria are resistant to standard therapeutic strategies, the need for alternative strategies arises. Since differential DNA methylation is often observed in pathogenic gene regulation, this study sought to assess the influence of DNA methylation (mediated by the *dam* gene) on antibiotic resistance regulation in UPEC strains and its potential as a therapeutic target. We knocked out the *dam* gene in selected UPEC strains via one-step allelic exchange, and assessed growth rate, susceptibility to antibiotics, and ability to form biofilms in the presence of antibiotics and oxidative stress in these *dam* mutants. To restore *dam* function, mutants were complemented with a plasmid containing the *dam* gene and the *qnrA* gene (where appropriate). The absence of DNA methylation among *dam* mutants was apparent: Δdam mutant cells were elongated and filamentous; had ≤ 2 -fold reduced growth rate, cell numbers and an extended lag phase (90-180 min). Further, there was an 8-fold decrease in resistance for strain cC119 versus cC119 Δdam against amoxicillin/clavulanic acid (AMC), trimethoprim/sulfamethoxazole (SXT) and gentamicin, and 4-fold against ciprofloxacin. Finally, there were increases in biofilm formation (including in the presence of oxidative stress) by the mutants relative to the parental strains. Phenotypic characteristics of parental strains were restored in *dam*-complemented strains. It was clear that the *dam* gene plays a vital role in DNA methylation and antibiotic resistance in UPEC strains.

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