Cysteine auxotrophy drives reduced susceptibility to quinolones and paraquat by inducing the expression of efflux-pump systems and detoxifying enzymes in S. Typhimurium

Villagra, Nicolás A.

Valenzuela, L. Matías

Mora, Aracely Y.

Millanao, Ana R.

Saavedra, Claudia P.

Mora, Guido C.

Hidalgo, Alejandro A.

Currently, Salmonella enterica serovar Typhimurium (S. Typhimurium), is a major global public health problem, which has caused food-borne illnesses in many countries. Today, with the extensive use of antimicrobials, antimicrobial resistance is increasing at a serious rate in S. Typhimurium isolates. The present study sought the role of cysteine (Cys) auxotrophy on the resistance to quinolones and paraquat in S. Typhimurium. Cys auxotrophy was achieved by deleting either the cysDNC, cysJIH or cysQ loci. Deletion of these loci resulted in loss of susceptibility against nalidixic acid, levofloxacin, ciprofloxacin (CIP) and paraquat. Further studies with cysJIH mutant indicated increased expression of multi-antibiotic resistance genes marA and ramA, and consequently increased expression of efflux-pump systems. The cysJIH mutant presented a smaller increase of reactive oxygen species (ROS) in presence of paraquat or CIP. Expression of katG and sodA (expressing for a catalase and a superoxide dismutase, respectively) genes was increased in presence of paraquat in the cysJIH mutant; while expression of the superoxide dismutase gene sodB was decreased. These results indicate that deletion of cysDNC, cysJIH or cysQ genes of S. Typhimurium renders Cys auxotrophy along with decreased susceptibility in response to quinolone and paraquat. Overexpression of efflux-pump systems AcrB-TolC and SmvA-OmpD and antioxidant enzymes KatG and SodA could explain the mechanisms of antimicrobial resistance in the Cys

auxotrophic mutants.