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DNA supercoiling activity of DNA gyrases from Francisella strains resistant to quinolones

Quinolones are one of the most commonly prescribed classes of antibacterials agents in the world and are used to treat several bacterial infections in humans. Accordingly, microbiological and clinical data showed that ciprofloxacin, and possibly other fluoroquinolones represent an efficient first-line treatment for oral therapy of tularemia, a disease caused by the Gram negative bacterium Francisella tularensis. These compounds inhibit DNA synthesis through interaction with complexes composed of DNA and either of the two target enzymes, DNA gyrase and topoisomerase IV that belong to type IIA topoisomerases.
A collection of fluoroquinolones resistant clones of Francisella was generated in our lab through an experimental evolution protocol applied on sensitive strains exposed to increasing fluoroquinolone concentrations. Exposure to antibiotic was accompanied by mutations in GyrA and GyrB. While some mutations were restricted to discrete regions of the so-called quinolone-resistance-determining regions (QRDR), amino acid substitutions or deletions never previously reported were also identified.
Here, our aim was to clarify the role of identified GyrA and GyrB mutations in fluoroquinolone resistance. Recombinant WT mutated GyrA and GyrB subunits from Francisella novicida and Francisella philomiragia were expressed in E. coli and purified as soluble proteins. Subsequently, the inhibitory effects of ciprofloxacin and moxifloxacin were evaluated against the functional activity of reconstituted DNA gyrase complexes. The data obtained demonstrated that, as in several bacterial species, the Asp87 residue of GyrA is a mutational hotspot conferring a high degree fluoroquinolone resistance in Francisella. Novel identified GyrA mutations including the conserved Pro43 residue are also implicated.

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