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## ST38 *E. coli* evolution in response to the natural conjugative plasmids carrying the carbapenemase gene *bla*<sub>OXA-48</sub>

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### Introduction and objectives

Carbapenems are last resort  $\beta$ -lactams used to treat multidrug resistant Gram-negative bacteria. However, the increased incidence of carbapenem resistance is threatening their therapeutic efficacy. The emergence of *E. coli* clones expressing carbapenemases and their dissemination in the community are particularly worrisome. Sequence Type (ST) 38 is the most prevalent ST among carbapenemase-producing *E. coli* isolated in France and in other European countries. By phylogenetic analysis, we showed the world-wide dissemination of at least three OXA-48 producing ST38 lineages with chromosomal integrations of the *bla*<sub>OXA-48</sub> gene, contrasting with the general mode of *bla*<sub>OXA-48</sub> dissemination in *Enterobacterales* through conjugative transfer of IncL pOXA-48 plasmids. We are aiming to characterize the benefit of chromosomal integrations and the involved mechanisms.

### Materials and methods

We introduced three different variants of pOXA-48 by conjugation into different naïve ST38 *E. coli* strains and assessed the fitness cost by monitoring growth in rich and poor media. We assessed the plasmid stability by ten days passages without selective pressure. We also performed a 28-day experimental evolution of the different transconjugants using meropenem as selective pressure to look for mutations that may lower potential fitness cost and to select *bla*<sub>OXA-48</sub> chromosomal integration. Evolved strains were analyzed by whole genome sequencing.

### Results, discussion and conclusion

The three pOXA-48 variants were unstable in three different ST38 *E. coli* genetic backgrounds. Particularly, growth curve analyses revealed a strong fitness decrease in one of these backgrounds with an up to 26% increase in generation time whatever the plasmid variant. *bla*<sub>OXA-48</sub> integrations into chromosome were observed during experimental evolution. They were dependent on both the genetic background of the transconjugant and on the pOXA-48 type and led to a fitness improvement. Alternatively, an increase in both the fitness of evolved transconjugants and in plasmid stability was reached in transconjugants inactivated or mutated in an operon of unknown function. We hypothesize that proteins encoded by this operon might interact with pOXA-48 plasmids. Altogether our results provide new information on the emergence of *E. coli* lineages expressing OXA-48 carbapenemases.

**Key words:** OXA-48, *E. coli* ST38, carbapenem resistance, plasmid stability, evolution