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Genetic basis of multidrug resistance in *Acinetobacter baumannii*

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SUMMARY

Acinetobacter baumannii has emerged as a significant bacterial pathogen pre-eminently associated with hospital-acquired infections. Strains of this species may currently exhibit resistance to nearly all or even all clinically relevant drugs. The vast majority of epidemic and multidrug-resistant *A. baumannii* strains belong to a few globally spread lineages, in particular to the so-called European (EU) clones I, II, and III. Complex resistance patterns displayed by these strains result from their marked capacity to develop, acquire, and combine secondary resistance mechanisms against originally effective agents. The aim of this thesis was to broaden our knowledge on the genetic basis and epidemiology of multidrug resistance in *A. baumannii*. The obtained results have been published in the form of six studies which are part of this thesis.

In the first study, we analysed the epidemiology of carbapenem resistance among hospital strains of *Acinetobacter* in the Czech Republic. We have shown that the emergence of this resistance was associated with the spread of *A. baumannii* strains of EU clone II and it was predominantly caused by the overexpression of the intrinsic $bla_{\text{OXA-51}}$-like gene. Furthermore, the striking variation in the susceptibility to other clinically relevant drugs in these strains appeared to result from both the horizontal spread of resistance genes (e.g. *aacC1*, *aphA6*, or $bla_{\text{TEM-1}}$) and differential expression of the AdeABC efflux pump.

The second and third studies dealt with the genotypic characterization of a high-level carbapenem resistant strain of *A. baumannii* imported to the Czech Republic from Egypt in 2011. The strain co-harboured genes encoding five ß-lactamases (NDM-1, OXA-23, OXA-51-like, TEM-1, and ADC) and at least five other resistance mechanisms, which made it resistant to all clinically relevant drugs except for colistin and tobramycin.

In the fourth study, we have identified and described a clinically relevant mechanism of sulbactam resistance in *A. baumannii* based on the production of the TEM-1 ß-lactamase. Its role was supported especially by the correlation between the level of sulbactam resistance and the expression of the $bla_{\text{TEM-1}}$ gene, by the transferability of sulbactam resistance via a $bla_{\text{TEM-1}}$-carrying plasmid, and by the susceptibility of a clinical strain expressing TEM-19, a low activity variant of TEM-1.

In the fifth and sixth studies, we investigated the structural diversity of AbaR genomic resistance islands in the population of *A. baumannii* EU clone I in order to find additional clues for a better understanding of the evolution of antibiotic resistance in this multidrug-resistant lineage. We have described nine novel AbaR islands which were truncated variants of AbaR3. These variants resulted either from IS*26*-mediated deletions or homologous recombination. We suggested that AbaR3 is the original form of AbaR in EU clone I, which may have provided strains of the lineage with a selective advantage facilitating their spread in European hospitals in the 1980s or before.