

“Elucidation of linezolid-resistance determinants in
Mycobacterium abscessus”

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Mycobacterium abscessus is notoriously known for its multidrug-resistant phenotype and linezolid is one of the antibiotics used to treat the *M. abscessus* infection. However, the linezolid-resistance mechanisms of this organism are not well-understood. The objective of this study was to identify possible linezolid-resistance determinants in *M. abscessus*. In this study, step-wise spontaneous mutants were selected from a linezolid-susceptible strain, M61 (MIC: 0.25 mg/L). Whole-genome sequencing and subsequent PCR verification of the resistant second-step mutant, A2a(1) (MIC: >256 mg/L), revealed three mutations in its genome, two of which were found in the 23S rDNA (g2244t and g2788t) and another one was found in a gene encoding the fatty-acid-CoA ligase *FadD32* (c880t → H294Y). The 23S rRNA is the molecular target of linezolid in a bacterial cell and mutations in this gene may alter the binding sites of the drug, leading to the development of resistance. Interestingly, the g2244t and g2788t mutations of the 23S rDNA gene, found in A2a(1), corresponds exactly to the g2270t and g2814t mutations which have previously been associated with the linezolid resistance in *M. tuberculosis*. Furthermore, PCR analysis revealed that the c880t mutation in the *fadD32* gene first appeared in the first-step mutant, A2 (MIC: 1 mg/L). Complementation of the wild-type M61 with the pMV261 plasmid carrying the mutant *fadD32* gene caused the previously sensitive M61 to develop a reduced susceptibility to linezolid (MIC: 1 mg/L). We hypothesize that the c880t mutation in this gene may alter the cell-wall permeability and affect the entry of linezolid, leading to the reduced susceptibility observed in the A2 mutant. In general, the findings of this study uncovered hitherto undescribed mechanisms of linezolid resistance in *M. abscessus* that may be useful for the development of novel anti-infective agents against this multidrug resistant pathogen.

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