Identification and characterization of Mabs_4780, a new determinant required for intracellular survival and pathogenicity of Mycobacterium abscessus

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Résumé

Mycobacterium abscessus (Mabs) is an emerging rapid-growing mycobacteria causing severe lung infections, particularly in cystic fibrosis patients. The smooth morphotype displays surface expression of glycopeptidolipids (GPLs) whereas the rough morphotype is characterized by the loss of surface GPL. Rough variants are involved in more severe clinical forms although the underlying physiopathological mechanisms remain obscure. We have recently developed a zebrafish embryo model to decipher the pathogenesis of Mabs and the chronology of the infection process.

Herein, we evaluated the contribution of MABS_4780 in rough Mabs virulence. A mutant was constructed in which MABS_4780 was disrupted by a hygromycin cassette. This strain exhibited a higher susceptibility to thiacetazone, a second-line antitubercular drug, compared to the parental strain and higher sensitivity to detergents, presumably due to alterations of cell wall composition/structure. Consistent with hypothesis, solving the three-dimensional structure of the M. smegmatis orthologue revealed a MaoC-like structure of known dehydratases, potentially involved in cell wall lipid biosynthesis. Since Amoeba may represent the environmental reservoir of Mabs, we also assessed the intracellular fate of the mutant in Acanthamoeba Castellanii. The mutant failed to replicate intracellularly but this growth defect was not due to a general metabolic abnormality since it grew similarly to parental strain in vitro. In addition, unlike the R variant, the mutant strain was extremely attenuated in infected zebrafish embryos and was unable to produce abscesses within the central nervous system and to kill the embryos.

Our findings demonstrate the unanticipated role of MABS_4780 in physiopathology of Mabs infection, emphasizing its potential as an attractive drug target.

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Mots-Clés: Mycobacterium abscessus, Zebrafish embryos, Mabs_4780, pathogenesis