Novel Path Towards Colistin Resistance In Pseudomonas Aeruginosa During Chronic Infection Involves Polymorphisms In Uncharacterized Glycosyltransferase Gene - DTU Orbit (08/11/2017)

Novel Path Towards Colistin Resistance In *Pseudomonas Aeruginosa* During Chronic Infection Involves Polymorphisms In Uncharacterized Glycosyltransferase Gene

Introduction: Antibiotic resistance development in the gram-negative bacterium *Pseudomonas aeruginosa* is an increasing problem. The effect of colistin, one of the few last resort drugs commonly given to cystic fibrosis (CF) patients, is dependent on the lipopolysaccharide (LPS) structure. We have identified a novel gene cluster, which is involved in colistin susceptibility in chronically infecting *P. aeruginosa* strains. The gene cluster contains two uncharacterized glycosyltransferases and a gene of unknown function. During chronic infection of CF patients one of the glycosyltransferase genes is prone to mutation. Methods: The glycosyltransferase single nucleotide polymorphism (SNP) was reverted to the reference genotype in a clinical isolate and in parallel introduced into the laboratory reference strain PAO1 to provide a clear background for mutational analysis. We evaluated minimal inhibitory concentration by microbroth dilution, virulence in an amoebae model and LPS structure by visualization in a silver-stained gel. Results: Reversion of the SNP to reference genotype resulted in increased colistin susceptibility, reduced virulence in an amoebae model and altered LPS structure. The results indicate that this glycosyltransferase polymorphism is needed for the clinical strain to be fully virulent. However, introducing the SNP into PAO1 did not result in altered phenotypes. These results reveal this uncharacterized glycosyltransferase as a novel *in vivo* path to colistin resistance by LPS modification. Conclusions: Colistin resistance development *in vivo* occurs via multiple paths. Here a novel pathway for the development of colistin resistance was described. It involves mutations in a hitherto uncharacterized glycosyltransferase.

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