

16S methylases in Gram-negative bacilli

Methylation of 16S ribosomal RNA (rRNA) has emerged as a novel aminoglycoside resistance mechanism in pathogenic gram-negative bacteria since 2003 and is increasingly reported worldwide. 16S rRNA methyltransferases (RMTs) are responsible for very high level resistance to various aminoglycosides. The coding genes are exogenously acquired and widely distributed among Enterobacteriaceae and non-glucose-fermenting bacilli of human and animal origin. The RMTs are classified into two subgroups, the N7-G1405 and the N1-A1408 RMTs, based on the mode of modification of 16S rRNA. Both add the methyl group of S-adenosyl-l-methionine to nucleotide G1405 or nucleotide A1408 at the A-site of 16S rRNA, which interferes with aminoglycoside binding to the target. Eight distinct genes, *rmtA*, *rmtB*, *rmtC*, *rmtD*, *rmtD2*, *rmtE*, *armA* and *npmA*, encoding their respective enzymes have been identified in clinical and veterinary strains from various geographic areas, including East Asia, Europe, North and South America and Oceania, since 2003. *NpmA* is the only enzyme among them that methylates residue A1408 and has been identified in a single *Escherichia coli* isolate in Japan, in 2007. *RmtE* is the lastly described RMT in 2010 and has been found in bovine-origin *E. coli* isolates. Some of these genes have been identified in glucose-fermenting and non fermenting species. For instance, *armA* has been found in both Enterobacteriaceae and *Acinetobacter baumannii* isolates and *rmtD* has been found in *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The genetic determinants responsible for RMT production are often mediated by mobile genetic elements like transposons which are embedded into various transferable plasmids. This genetic apparatus may thus contribute to the rapid worldwide dissemination of the resistance mechanism among pathogenic microbes. One great concern is the multidrug resistance development in RMT-producing pathogenic bacteria through further accumulation of various antimicrobial resistance genes such as carbapenem-hydrolyzing beta-lactamases. More worrisome is the emergence of members of Enterobacteriaceae family coproducing NDM-1 metallo-beta-lactamase and RMTs (*RmtB*, *RmtC* and *ArmA*) often located on the same broad-range conjugative plasmid. Thus far, RMTs have been reported from at least 30 countries or regions. The worldwide dissemination is becoming a serious global concern and this implies the necessity to continue investigations on the trend of RMTs to restrict their further distribution.