Epigenetic Mode of Bacterial Drug Resistance

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Received date: January 20, 2017; Accepted date: January 21, 2017; Published date: January 23, 2017

Abstract

Bacterial drug resistance is one of the major factors which plays a crucial role in the treatment. Bacteria evolved various mechanisms to evade the action of these antibiotics. One of the strategies is the prevention of binding of antibiotics to ribosome through addition of methyl group favored by different methyltransferase enzymes. Ribosomal methylation leads to development of multi-drug resistant organisms, which are resistant to different classes of antimicrobial agents. Development of antibiotic resistance due to the ribosomal methylation raise concerns about the future clinical efficacy of several antimicrobial classes.

Keywords: Multi-drug resistant; Antimicrobial agents; Drug resistance; Erythromycin resistant

Introduction

Antibacterial drugs are regarded as the antidote for the infections. These antibiotics has been used widely over several decades all over the world. The discovery of antibiotics saved several million lives worldwide. Unfortunately, the bacteria has developed several mechanism of drug resistance and are known to spread across the globe. Several bacterial isolates including gram positive bacteria such as Methiclllin Resistant Staphylococcus aureus (MRSA), vancomycin resistant enterococci (VRE) and carbapenem drug resistant gram negative bacteria including Enterobacteriacaeae, Pseudomonas aeruginosa and Acinetobacter Sp are known to cause infections leading to high morbidity and mortality [1].

The bacteria has developed several mechanism to avoid the action of antibiotics including inactivation or modification of the antibiotics, alteration in the target site leading to the ineffective binding of the antibiotics, modification of the metabolic pathways and reduced intracellular accumulation of antibiotics due to the increased affinity of the antibiotics using afflux pumps. It has been known that major target site for the antibiotic actions is ribosomal region including decoding center of the 30S subunit, peptidyltransferase centre, GTPase centre and 50S subunit. Bacteria evolved a elegant way of preventing of the binding of the antibiotics to the ribosomal region by the addition of the methyl group to rRNA favored by methyltransferase enzymes, this methylation prevents the binding of different classes of drugs leading to the development of the drug resistance [2].

Antibiotic resistance to due to methylation at 23S rRNA

Several methyltransferase enzymes promote the binding of methyl group to 23S rRNA employing S-adenosyl-L-methionine as a cofactor. The erythromycin resistant gram positive bacteria were resistant to unrelated class of antibiotics including lincosamide and streptogramin B, due to the expression of the EmrC RNA methyltransferase that causes N-6 dimethylation of adenine at a position of 2058 in 23S rRNA. Several erm methyltransferases have been detected to confer drug resistance through methylation of 23S rRNA.

The aviRa gene encode rRNA methyltransferase gene, methylates the V domain region of the 23S rRNA and confer resistance to the avilamycin. The cfr (chloromphenicol/ florfenicol) gene promotes the methylation at A2503 region of 23S rRNA and confers drug resistance to five different classes of antibiotics including phenicol, lincosamide, oxazolidinone, pleuromutilin, and streptogramin as well as to macrolides. Studies have shown the presence of cfr and development of multidrug resistance and were isolated from bacterial isolates derived from the nosocomial infections making them a potent source for the spread of multidrug resistance. Similarly several other genes encoding the methyltransferase enzymes were discovered which confer the drug resistance through the methylation of 23SrRNA. The emtA a rRNA methyltransferase confers methylation at the residue of the G2470 leading to the development of high drug resistance to the evernimicin. The rlmA encodes methylation at G748 region conferring drug resistance to the tylosin and tsr gene leads to the development of drug resistance to the thiostrepton due to methylation at A1067 region at the position of 2'-O-ribose of 23S rRNA. The drug resistance due to 23S rRNA has been reported worldwide. Along with 23S rRNA, methylation to 16S rRNA also seen promoting drug resistance [3].
Antibiotic resistance to methylation at 16S rRNA

Methylation of the 16S rRNA has been emerged as a drug resistant mechanism especially in gram negative bacteria against aminoglycosides. Studies have been carried out and found several methyltransferases encoded by several genes including armA, rmtA, rmtB, rmtC, rmtB, rmtE and npmA add a methyl group to 16S rRNA. Most of these methyltransferases post-transcriptionally methylate residue G1405 of 16S rRNA resulting in high-level resistance to gentamicin, tobramycin, amikacin, and plazomicin. The drug resistance due to 16S rRNA has been reported worldwide without any regional distribution. The direct clinical impact due to the presence of these methyltransferase enzymes leading to the aminoglycoside drug resistance has to be determined to ascertain the treatment options [4].

Discussion

The development of drug resistance to several classes of antibiotics due to the methylation at the ribosomal region is a worrisome in the treatment. Several studies have shown the outbreak of multi-drug resistant organisms for example the isolation of Staphylococcus aureus which is resistant to linezolid having the cfr gene which confers drug resistance to different classes of antibiotics. The potential dissemination of these genes among clinical isolates may lead to rapid simultaneous increase in the resistance for several antibacterial classes. Development of antibiotic resistance due to the ribosomal methylation raise concerns about the future clinical efficacy of several antimicrobial classes.

Research work are going on to circumvent the methylation mode of drug resistance including designing new antibiotics which are not affected by methylation, or inactivation of methyltransferase enzymes through novel peptides. To conclude a deeper understanding the mode of action of these methyltransferases, along with enhancing the research work to develop drugs to overcome the ribosomal methylation mode of drug resistance pave a way for better outcome of the treatment.

References