Aminoglycoside Resistance

The Emergence of Acquired 16S Ribosomal RNA Methyltransferases

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KEYWORDS

- Aminoglycoside • 16S ribosomal RNA • Posttranscriptional methylation
- Carbapenemease

KEY POINTS

- Aminoglycoside-producing Actinobacteria produce 16S ribosomal RNA methyltransferase (16S-RMTase) to protect themselves.
- High-level aminoglycoside resistance caused by production of acquired 16S-RMTase in pathogenic gram-negative bacteria was first reported in the early 2000s.
- Bacteria that produce 16S-RMTases frequently coproduce ESBL, and more recently, carbapenemase, especially NDM-1.
- Spread of 16S-RMTase-producing bacteria further compromises the already limited treatment options for infections caused by MDR/XDR pathogens.

INTRODUCTION

Antimicrobial resistance has been recognized as one of the most pressing public health and societal issues of our times. The problem is most acute in gram-negative bacteria, where strains resistant to multiple (multidrug-resistant [MDR]) or almost all (extensively drug-resistant [XDR]) available agents are emerging.[1] Of particular concern has been the spread of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae in the 1990s, which was followed closely by the emergence and rapid dissemination of carbapenemase-producing organisms.

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The three key classes of antimicrobial agents with gram-negative activity include β-lactams (especially β-lactam-β-lactamase inhibitor combinations, later-generation cephalosporins, and carbapenems), fluoroquinolones, and aminoglycosides. Aminoglycosides were identified through systematic screening of soil Actinobacteria that started in the 1940s. The first aminoglycoside streptomycin was discovered from *Streptomyces griseus* and successfully used for the treatment of tuberculosis and then infections with gram-negative bacteria. A typical aminoglycoside possesses an amino-containing or non-amino-containing sugars linked to six-membered rings with amino group substituents, hence the name aminoglycoside. Numerous aminoglycosides have since been identified or semisynthesized and used in clinical practice.

Aminoglycosides are grouped into 4,6-disubstituted 2-deoxystreptamine (DOS), 4,5-disubstituted DOS, and 4-monosubstituted DOS based on their chemical structures (**Figs. 1** and **2**). Representative 4,6-disubstituted DOS agents include gentamicin, tobramycin, and amikacin, which are widely used as intravenous or nebulized formulations for the treatment of infections caused by gram-negative bacteria (usually in combination with a β-lactam agent), gram-positive bacteria (for synergistic activity with a β-lactam or peptidoglycan), and atypical mycobacteria (again in combination with other active agents). 4,5-Disubstituted DOS agents, represented by neomycin, are limited in their utility by toxicity and are administered either orally or topically but not intravenously. Monosubstituted DOS agents are represented by apramycin, which is used in veterinary medicine.

MECHANISMS OF AMINOGLYCOSIDE RESISTANCE

Aminoglycosides bind to the aminoacyl-tRNA recognition site (A-site) of the 16S rRNA that constitutes the 30S ribosomal subunit, leading to inhibition of polypeptide synthesis and subsequent cell death. Resistance to aminoglycosides may occur based on several mechanisms: (1) enzymatic modification and inactivation of the aminoglycosides, mediated by aminoglycoside acetyltransferases, nucleotidyltransferases, or phosphotransferases and commonly observed across gram-positive and -negative bacteria[2,3]; (2) increased efflux; (3) decreased permeability; and (4) modifications of the 30S ribosomal subunit that interferes with binding of the aminoglycosides. For the latter, both mutations (nucleotide replacement) and posttranscriptional modifications have been associated with aminoglycoside resistance. Examples include point mutations in the 16S rRNA and the *rpsL* gene encoding the S12 protein in *Mycobacterium tuberculosis* leading to streptomycin resistance.[4] However, mutations within the 30S ribosomal subunit do not seem to be a common aminoglycoside resistance mechanism among fast-growing pathogenic bacteria in general.

However, posttranscriptional modification of the 16S rRNA is commonly observed among aminoglycoside-producing Actinobacteria, including *Streptomyces* spp and *Micromonospora* spp, which are naturally resistant to these metabolites of their own. This process is mediated by posttranscriptional methylation of either the N-7 position of nucleotide G1405 or the N-1 position of nucleotide A1408 on the 16S rRNA by various 16S rRNA methyltransferases (16S-RMTases) (**Fig. 3**).[5] Intrinsic N7-G1405 16S-RMTases are found in both *Streptomyces* spp and *Micromonospora* spp, whereas intrinsic N1-A1408 16S-RMTases have only been identified in *Streptomyces* spp.[6] N7-G1405 16S-RMTases confer resistance to 4,6-disubstituted DOS agents, such as gentamicin, tobramycin, and amikacin, but not 4,5-disubstituted and monosubstituted DOS agents. In contrast, N1-A1408 16S-RMTases are capable of conferring resistance all these groups.