Antibiotics that affect the ribosome

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Summary

The ribosome is a major bacterial target for antibiotics. Drugs inhibit ribosome function either by interfering in messenger RNA translation or by blocking the formation of peptide bonds at the peptidyl transferase centre. These effects are the consequence of the binding of drugs to the ribosomal subunits. Various mechanisms, including enzymatic detoxification, target alteration (ribosomal [r]RNAs and ribosomal proteins) and reduced accumulation (impermeability and efflux) are involved in bacterial resistance to protein synthesis inhibitors. The fact that some positions in rRNA participate in the binding of antibiotics belonging to distinct families explains why bacteria have developed mechanisms that can lead to cross-resistance.

Keywords

16S rRNA – 23S rRNA – Aminoglycoside – Fusidic acid – Macrolide – Orthosomycin – Oxazolidinone – Phenicol – Pleuromutilin – Protein synthesis – Ribosomal protein – Ribosome – Tetracycline.

Introduction

Various classes of antibiotic target the ribosome, and they play an important role in human and veterinary medicine. These agents will be presented with respect to their mechanism of action.

30S ribosomal subunit inhibitors

The 30S is the smaller subunit of the ribosome of prokaryotes. It is a complex structure formed of 16S RNA and ribonucleoproteins that functions in messenger (m)RNA translation and is inhibited by aminoglycosides and tetracyclines.

Aminoglycosides

Aminoglycosides are isolated from antibiotic producers such as *Streptomyces* or *Micromonospora*, and are thus respectively named with the suffix '-mycin' or '-micin'. They include major drugs used in human and veterinary medicine and are composed of a 6-carbon aminocyclitol ring (2-deoxystreptamin in many instances) linked by glycosidic bonds to one or more sugar derivatives. Based on their structure they are classed in various groups. Amikacin, gentamicin and tobramycin are the major aminoglycosides used in human clinical settings, whereas apramycin and fortimicin are reserved for veterinary medicine. Aminoglycosides possess a broad antibacterial spectrum including Gram-negative and Gram-positive bacteria, but not anaerobes. They exert a rapid bactericidal effect against target bacteria. The bactericidal effect is unusual among protein synthesis inhibitors and results in their capacity to induce oxidative stress.

Mode of action

Aminoglycosides inhibit bacterial protein synthesis by pleiotropic actions that lead to the alteration of translation at diverse steps including initiation, elongation and termination (4). It has been known for many years that aminoglycosides bind to the 30S ribosomal subunit; more recent studies have identified their target as the 16S ribosomal (r)RNA and particularly the decoding A-site for the 4,6-substituted 2-deoxystreptamine (2-DOS) (5). This binding stabilises a normal mismatch in codon–anticodon pairing, leading to mistranslations. Adenine 1408 of 16S RNA is crucial for binding, and the presence of a guanine at the homologous position of 18S RNA explains the natural resistance of eukaryotes to 4,6-substituted 2-DOS.

Resistance mechanisms

The main resistance mechanism to aminoglycosides in pathogenic bacteria is due to enzymatic detoxification. Target alteration of 16S RNA or of certain ribosomal proteins and reduced uptake or export are also found (4).

Enzymatic modification

Three classes of enzyme, aminoglycoside *O*-phosphotransferases (APH), *O*-nucleotidyltransferases (ANT) and *N*-acetyltransferases (AAC), are involved in detoxification (13). Subclasses are defined by the position of the catalytic site, at a hydroxyl group (APH and ANT) or at an -NH$_2$ group (AAC), which is made available or not according to the structure of the compound. Distinct enzymes within a subclass can share a substrate profile, while the same aminoglycoside can be modified by different enzymes. The combination of various enzymes is usual, and the phenotype results from the addition of each mechanism. Except for rare examples, the genes encoding these enzymes are part of plasmids or transposons. It is important to note that the distribution of the various modifying enzymes is specific to either Gram-positive or Gram-negative bacteria (1, 5). The most common modifying enzymes are summarised in Tables I and II. Streptomycin and spectinomycin are structurally unrelated to other aminoglycosides, and therefore they are inactivated by different enzymes, including APH(3″), APH(6), ANT(3″)(9) and ANT(6) in the case of streptomycin, and ANT(3″)(9) and ANT(9) in the case of spectinomycin. The APH(3″) and APH(6) are specific for Gram-negative bacteria and are encoded by the *strA* and *strB* genes found in a transcriptional unit.

Target alteration

Mutation in 16S ribosomal RNA
More than 50% of the ribosomes must be altered for resistance to occur. The fact that the rRNA operon (*rrn*) is present in several copies in most bacteria (six in *Escherichia coli*) limits the impact of this mechanism to bacteria with a single copy of the rRNA operon, such as *Mycobacterium* spp.

Mutation in ribosomal proteins
Mutations in the S12 protein have been reported in spontaneous mutants resistant to streptomycin, among both Gram-positive and Gram-negative bacteria. This mechanism is not found with other aminoglycosides, except for the spectinomycin resistance in *Pasteurella multocida* that is caused by a mutation in the S5 protein.

Methyltransferases
This mechanism, first described in antibiotic producers, was more recently reported in Gram-negative human pathogens. Two positions are involved in methylation: G1405 and A1408. ArmA, RmtA, RmtB, RmtC, RmtD and RmtE correspond to G1405 methyltransferases that confer high-level resistance to amikacin, fortimicin, gentamicin and tobramycin, but not to neomycin, which is a 4,5-substituted 2-DOS. The A1408 methyltransferase NmpA is extremely rare and confers, in addition, resistance to apramycin.

Table I
Substrate profiles of the main aminoglycoside-modifying enzymes in Gram-positive bacteria

	APH(3′)-III	ANT(4′)-I	APH(2″)-AAC(6′)
Kanamycin B	+	+	+
Gentamicin	–	–	+
Tobramycin	–	+	+
Amikacin	+	+	+
Apramycin	–	–	–
Fortimicin	–	–	–

AAC: aminoglycoside *N*-acetyltransferase
ANT: aminoglycoside *O*-nucleotidyltransferase
APH: aminoglycoside *O*-phosphotransferase

Table II
Substrate profiles of the main aminoglycoside-modifying enzymes in Gram-negative bacteria

	APH(3′)	AAC(3)	AAC(6′)	ANT(4′)	ANT(2″)
Kanamycin B	+		+	+	+
Gentamicin	–	+	(–)[a]	–	+
Tobramycin	–	+	+	+	+
Amikacin	(–)[b]	–	+	+	–
Apramycin	–	(–)[c]	–	–	–
Fortimicin		(–)[c]	–	–	–

a) Gentamicin is modified by AAC(6′)-II
b) Amikacin is a substrate for APH(3′)-VI
c) Apramycin is modified by AAC(3)-IV and fortimicin by AAC(3)-I
AAC: aminoglycoside *N*-acetyltransferase
ANT: aminoglycoside *O*-nucleotidyltransferase
APH: aminoglycoside *O*-phosphotransferase

Impaired uptake

Alteration of the respiratory chain gives rise to small colonies with decreased susceptibility to all aminoglycosides. Efflux systems such as AcrD, AdeABC and MexXY are involved in moderate resistance to aminoglycosides in *E. coli*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, respectively.

Tetracyclines

Tetracyclines are closely related structurally, with a four-ring carbocyclic skeleton that results from the biosynthesis of polyketides by bacterial type II polyketide synthases produced by *Streptomyces*. They display a broad spectrum of activity, including Gram-positive and Gram-negative bacteria. They have an important role in both human and veterinary medicine, in particular against intracellular pathogens such as *Brucella*, *Chlamydia* and *Rickettsia*. The most commonly used tetracyclines in domestic

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animals are oxytetracycline and chlortetracycline. Tigecycline is the first clinically available drug among the glycylcyclines. Tigecycline is a minocycline derivative with a substitution that increases the spectrum of activity. This compound can be effective against multidrug-resistant Gram-negative bacteria such as pan-resistant strains of *A. baumannii.*

Mode of action

Tetracyclines inhibit protein synthesis by impairing the stable binding of aminoacyl-transfer (t)RNA to the bacterial ribosomal A-site (3).

Resistance mechanisms

The widespread use of tetracyclines in humans, other animals, and agriculture throughout the world has contributed to the emergence of resistance to these antibiotics in commensal and pathogenic bacteria resulting from the acquisition of *tet* genes. Two mechanisms are involved in tetracycline resistance. The first is due to efflux proteins, including Tet(A), Tet(B), Tet(C), Tet(D), Tet(E), Tet(G), Tet(H) and Tet(Z), which reduce the intracellular drug concentration; except for Tet(B) most of these determinants do not confer resistance to minocycline. All but Tet(Z) are confined to Gram-negative bacteria (3). The second mechanism results from ribosomal protection and confers resistance to tetracycline and minocycline. The ribosomal protection proteins have homology with elongation factors EF-TU and EF-G. Tet(M) and Tet(O) are the most studied and Tet(M) has been found in numerous bacterial species including Gram-positive and Gram-negative bacteria.

In most instances expression of the resistance is regulated by tetracycline. Efflux determinants are controlled by a repressor protein interacting with tetracycline, whereas ribosomal protection is generally regulated by tetracycline via transcriptional attenuation, as demonstrated for Tet(M). Furthermore, it has been shown that the presence of tetracyclines can increase the horizontal transfer of the genes that are responsible for its own resistance.

Other efflux systems, in particular several belonging to the Resistance–Nodulation–cell Division (RND) family, have also been reported to contribute to tetracycline resistance as a result of overexpression due to mutation in their regulatory sequences.

In addition, mutations in 16S rRNA have been reported in several microorganisms with a low number of copies of the rRNA (*rrn*) operon, such as *Helicobacter pylori.*
Neither efflux mediated by Tet(A) and related systems nor ribosomal protection determinants confer resistance to tigecycline. However, failure during treatment with tigecycline has been reported to be a result of the overexpression of intrinsic pumps, such as AdeABC in

A. baumannii, which in this case follows mutation of the two-component regulatory system that governs the expression of the *adeABC* operon.

50S ribosomal subunit inhibitors

The 50S is the larger subunit of the 70S ribosome of prokaryotes. It consists of 5S and 23S RNA and 30 ribosomal proteins. The secondary structure of 23S rRNA is divided into six large domains. The domain V is of particular interest because of its peptidyl transferase activity. Macrolides and related compounds, such as chloramphenicol, fusidic acid, pleuromutilins, the orthosomycin group and oxazolidinones, are various families of protein synthesis inhibitor that interfere with the 50S subunit.

Macrolides and related compounds

Macrolides, lincosamides and streptogramins (MLS) are compounds that are distinct structurally but share a common mode of action and show similar antibacterial spectra, including staphylococci, streptococci, mycoplasmas and campylobacters (6). These antibiotics are produced by *Streptomycetes* by means of various types of polyketide synthase.

Macrolides are classified on the basis of the number of atoms in the ring of the macrocyclic lactone (12 to 17), to which are attached deoxy sugars (desosamine and cladinose).

The 14-membered rings include clarithromycin, erythromycin, roxithromycin, and ketolide semi-synthetic derivatives such as telithromycin.

The 15-membered rings include azithromycin, a semi-synthetic derivative of erythromycin with a methyl-substituted nitrogen atom incorporated into the lactone ring. This compound is largely used in human medicine and exhibits a similar spectrum to that of erythromycin, with increased activity against Gram-negative bacteria.

The 16-membered rings include josamycin, midecamycin, spiramycin and tylosin. Lincosamides are devoid of the lactone ring and consist of lincomycin and clindamycin, its improved derivative.

Streptogramins include streptogramin A (dalfopristin, pristinamycin IIA, virginiamycin M) and streptogramin B (pristinamycin IA, quinupristin, virginiamycin S). The A and B components act synergistically, for example pristinamycin IA + IIA, quinupristin–dalfopristin, and virginiamycin M + S.

Mode of action

These antibiotics bind to the 23S rRNA, close to the peptidyl transferase centre of the 50S subunit, which catalyses formation of peptide bonds during elongation. They block extension of the peptide chain and lead to dissociation of peptidyl-tRNA (6).

As already mentioned, macrolides and related compounds are essentially active against Gram-positive bacteria; however, certain Gram-negative bacteria such as *Helicobacter*, *Legionella* and intracellular microorganisms are part of the activity spectrum. In contrast, efflux pumps are responsible for the natural resistance of enterobacteria to these drugs and for the resistance of *Enterococcus faecalis* to lincosamides and streptogramin A. Clarithromycin has the advantage of activity against *Mycobacterium avium*.

Resistance mechanisms

Three major mechanisms are involved in acquired resistance to MLS. The first consists of alteration of the ribosomal target, either by 23S rRNA methylation, or by mutations in 23S rRNA or proteins of the 50S subunit.

Alteration of the 50S subunit

Methylation of 23S ribosomal RNA

Methylation, in particular at adenine 2058, which plays a role in the binding of MLS, is responsible for a cross-resistance designated MLS_B. Methylation is due to Erm enzymes, and more than 30 proteins have been reported (faculty.washington.edu/marilynr/). The expression of *erm* genes is either inducible, and regulated by translational attenuation, or constitutive. The ability of macrolides to induce the genes depends on their structure; those with a 14-atom lactone ring, except ketolides, are strong inducers and these include erythromycin. Monomethylation at A2058 confers a low level of resistance to erythromycin whereas dimethylation leads to high resistance. Interestingly, resistance to tylosin and mycinamycin requires methylation at two distinct positions, G748 and A2058 (7).

Mutation of the 50S subunit

Mutations of the 23S rRNA at several crucial positions have been reported in *M. avium* and *H. pylori* possessing one and two copies of the rRNA (*rrn*) operon, respectively. Mutations in ribosomal proteins L4 and L22 have also been involved in resistance.

Enzymatic modification

Erythromycin is inactivated by esterases and phosphotransferases (encoded by *ere* and *mph* genes, respectively). Lincosamides are inactivated by nucleotidyltransferases (*lnu* determinants), whereas streptogramin A and B are modified by acetyltransferases (*vat*) and lyases (*vgb*), respectively (6).

Efflux

Efflux is responsible for the natural resistance to MLS of Gram-negative bacteria. Among ATP-binding cassette (ABC) transporters and the major facilitator superfamily (MFS), certain members are involved in acquisition of resistance to MLS in Gram-positive bacteria. For example, *msrA* encodes an ABC transporter in staphylococci and *mefA* an MFS pump in streptococci. The main mechanisms of resistance to MLS in Gram-positive bacteria are summarised in Table III.

Table III

Main acquired mechanisms of resistance to macrolides, lincosamides and streptogramins in Gram-positive bacteria

Resistance mechanism		14-, 15-M[a]	16-M	L	S
23S rRNA methylation					
erm	inducible	R	S	S	S
	constitutive	R	R	R	S
Efflux					
ABC *msr*(A)[b]		R	S	S	S
MFS *mef*(A)[c]		R	S	S	S
Enzymatic modification					
lnu [d]		S	S	S/R	S
Enzymatic modification and efflux					
vat, vga, vgb		S	S	S/I	R

a) 14- and 15-lactone ring members of the macrolides (except telithromycin, the activity of which is only weakly reduced)

b) *msr*(A) is an ATP-binding cassette transporter found in staphylococci

c) *mef*(A) is an MFS family efflux pump essentially found in streptococci

d) *lnu* genes encode nucleotidyltransferases which confer resistance to lincomycin but not to clindamycin

lnu(A) is specific to staphylococci whereas *lnu*(B), *lnu*(C) and *lnu*(D) were reported in *Streptococcus agalactiae* and *S. uberis*

ABC: ATP-binding cassette

MFS: major facilitator superfamily

rRNA: ribosomal RNA

Pleuromutilins

Pleuromutilins are derivatives produced by the fungus *Pleurotus mutilus*; they include tiamulin and valnemulin, used to treat swine dysentery and pneumonia in pigs and poultry. Retapamulin is another derivative, developed for human topical use.

Mode of action

These drugs have been described as binding to domain V of 23S rRNA and blocking peptide formation (8, 9). Tiamulin has excellent activity against staphylococci, anaerobic bacteria, *Mycoplasma* spp., and intestinal spirochaetes.

Resistance mechanisms

Mutations in the ribosomal protein L3 and 23S rRNA have been associated with tiamulin resistance in *Brachyspira* spp.

The Cfr methyltransferase, which methylates the 23S rRNA nucleotide A2503 at the peptidyl transferase centre, confers combined resistance to phenicols, lincosamides, 16-membered macrolides, oxazolidinones, pleuromutilins and streptogramin A (10).

Orthosomycins

These antibiotics contain in their structure one or more orthoester linkages between carbohydrate residues; they include flambamycin, everninomycins, hygromycin and avilamycin. These compounds are produced by *Streptomyces* spp. and *Micromonospora* spp. They display a broad range of activity against Gram-positive bacteria, including glycopeptide-resistant enterococci and meticillin-resistant staphylococci, and some Gram-negative bacteria.

Avilamycin was used in Europe as a growth promoter in animal feeds before it was banned by the European Community; this antibiotic displays cross-resistance with everninomycins.

Mode of action

These drugs inhibit translation by binding to the 50S ribosomal subunit.

Resistance mechanisms

Resistance to these drugs involves methylation of specific nucleotides within domain V of 23S rRNA, as demonstrated with EmtA in *Enterococcus faecium* or AviRa and AviRb in the avilamycin producer (14). Mutations in the peptidyl transferase domain of 23S rRNA and amino acid substitution in ribosomal protein L16 have also been reported.

Phenicols

Chloramphenicol and its derivatives, thiamphenicol and florfenicol, are bacteriostatic antimicrobials with a broad spectrum of activity. Chloramphenicol was first obtained from *Streptomyces venezuelae* before it was synthesised. As a result of its bone marrow toxicity chloramphenicol is now very rarely used in medicine, except for the treatment of brain abscesses and eye infections, or in developing countries because it is inexpensive. Thiamphenicol is used in several countries in human medicine or as a veterinary antibiotic. The advantage of thiamphenicol is that, despite its inhibitory effect on the red cell count, it has never been associated with aplastic anaemia. However, florfenicol does carry the risk of aplastic anaemia. Florfenicol is used for the treatment of bovine respiratory disease because of its activity against *Mannheimia haemolytica*, *P. multocida* and *Histophilus somni*. It is also active against some chloramphenicol-resistant bacteria.

Mode of action

Phenicols prevent protein chain elongation by inhibiting the peptidyl transferase activity of the bacterial ribosome. Chloramphenicol binds specifically to nucleotides within the central loop of domain V of the 23S rRNA, preventing peptide bond formation. Ribosomal proteins L16 at the A-site and L2 and L27 at the P-site also participate in binding.

Resistance mechanisms

Chloramphenicol (and thiamphenicol) resistance is mainly due to enzymatic modification by chloramphenicol acetyltransferases (CAT) (12). These enzymes covalently link an acetyl group from acetylCoA to chloramphenicol, preventing it from binding to the ribosomes, and are grouped into two types, -A and -B. However, these enzymes do not confer resistance to florfenicol. They are encoded by various genes, which have been found on chromosomes, plasmids, transposons, or integron cassettes.

The second mechanism consists of efflux pumps encoded in Gram-negative bacteria by *cml* genes, which confer cross-resistance to chloramphenicol and florfenicol (12).

Interestingly, the *cat* and *cml* genes encode proteins with two unrelated functions, which are inducible by chloramphenicol. These genes are regulated by translational attenuation via a conserved leader peptide.

Other efflux systems, in particular the RND pumps of Gram-negative bacteria and the MFS of Gram-positive species, can also contribute to chloramphenicol resistance.

Furthermore, other uncommon mechanisms of resistance, such as phosphotransferases, porin alteration, mutation in the 23S binding site, and the Cfr methyltransferase, have also been described.

Fusidic acid

This sterol compound isolated from the fungus *Fusidium coccineum* is effective against Gram-positive bacteria such as *Staphylococcus* spp., *Streptococcus* spp. and *Corynebacterium* spp. The drug is not licensed for use in the United States, but it is used in Europe and Australia for treatment of staphylococcal infections.

Mode of action

Fusidic acid inhibits bacterial protein synthesis by preventing the turnover of elongation factor G (EF-G) in the ribosome.

Resistance mechanisms

The main mechanism is due to mutations in the EF-G-encoding gene *fusA*. The plasmid determinants *fusB* and *fusC* encode proteins that have a protective effect on EF-G, while *fusD* is responsible for the intrinsic fusidic acid resistance of *Staphylococcus saprophyticus* (2). A small-colony variant of *S. aureus* resistant to fusidic acid was reported to be a mutant with alteration of the L6 ribosomal protein. Finally, other mechanisms, such as efflux pumps in Gram-negative bacteria or group I chloramphenicol acetyltransferase, can also contribute to fusidic acid resistance (2).

Oxazolidinones

Oxazolidinones are synthetic compounds containing 2-oxazolidone in their structure. Linezolid is the unique member of this class, currently used for the treatment of skin and soft tissue infections in humans, although others are in development. Given its potent activity, linezolid has become an alternative to vancomycin to treat infections due to meticillin-resistant *S. aureus*.

Mode of action

Oxazolidinones bind to the 50S subunit, preventing formation of the initiation complex for protein synthesis. This mode is distinct from those of other protein synthesis inhibitors, which either block peptide extension or induce misreading of mRNA. The binding of oxazolidinones to nucleotides within the 23S rRNA V domain has been established (11).

Resistance mechanisms

Ribosomal alteration is responsible for the acquisition of resistance.

Mutation

The propensity for bacteria to develop resistance to linezolid is minimised because: (i) the majority of ribosomes are required to be altered; (ii) rRNA (*rrn*) often occurs in multiple copies. However, resistance has been observed to occur slowly in *E. faecalis* (four *rrn* copies) and in *S. aureus* (five or six copies). It has been established that various nucleotide substitutions within the peptidyl transferase loop of domain V of 23S rRNA can lead to linezolid resistance. Mutations have been investigated in *Mycobacterium smegmatis*, and more than ten positions have been involved. Although the ribosomal proteins L3 and L4 are not in the vicinity of the binding region, certain mutations in these proteins are associated with resistance.

Methyltransferase

A transferable mechanism due to Cfr methyltransferase has recently emerged. As already mentioned, this determinant confers cross-resistance to phenicols, lincosamides, oxazolidinones, pleuromutilins and streptogramin A (10).

Conclusion

Protein synthesis is a complex process, in which the ribosome plays a key role. Knowledge of ribosome structure allows the elucidation of its function and the mode of drug interaction. Several major classes of antibiotic inhibit protein synthesis by binding specifically to the 30S or 50S ribosomal subunits. Although rRNA is the major target for binding, ribosomal proteins can also play a crucial role. Bacterial resistance to these drugs is in most instances acquired by several mechanisms, including:

– mutations leading to nucleotide substitution in rRNA or amino acid substitution in ribosomal proteins, both involved in binding

– methylation of rRNA at critical positions

– direct enzymatic inactivation of the antibiotic

– impermeability or efflux.

Methyltransferases and modifying enzymes are mostly borne by mobile elements, and for that reason they represent a potential risk of dissemination. Resistance to antibiotics is a major challenge for the future; however, the characterisation of the processes developed by bacteria leads to the opportunity to circumvent these mechanisms by improving the currently available antibiotics.

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Antibiotiques agissant sur le ribosome

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Résumé
Le ribosome bactérien est une cible majeure des antibiotiques. Ces médicaments agissent en inhibant la fonction du ribosome essentiellement en interférant avec la traduction de l'ARN messager ou en bloquant la formation du pont peptidique au niveau du centre de la peptidyl transférase. Ces effets sont la conséquence de leur fixation sur les sous-unités du ribosome. Divers mécanismes incluant la détoxification enzymatique, l'altération de la cible (ARN ribosomaux et protéines ribosomales), et la réduction de l'accumulation (imperméabilité et efflux) sont impliqués dans la résistance bactérienne aux inhibiteurs de la synthèse protéique. Le fait que certaines positions de l'ARN ribosomal participent à la fixation d'antibiotiques appartenant à différentes familles explique que les bactéries ont developpé des mécanismes de résistance croisée.

Mots-clés
16S rRNA – 23S rRNA – Acide fusidique – Aminoglycoside – Macrolide – Orthosomycin – Oxazolidinone – Phénicol – Pleuromutilin – Protéine ribosomale – Ribosome – Synthèse protéique – Tétracycline.

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Antibióticos que actúan sobre el ribosoma

T. Lambert

Resumen
El ribosoma bacteriano es una de las dianas importantes de los antibióticos. Un fármaco puede inhibir la función ribosómica ya sea obstaculizando la traducción del ARN mensajero (ARNm) o bloqueando la formación de enlaces peptídicos en el centro peptidil-transferasa. Estos efectos vienen dados por la unión del fármaco con las subunidades ribosómicas. Varios son los mecanismos que intervienen en la resistencia bacteriana a los inhibidores de la síntesis proteínica; detoxificación enzimática, alteración de la diana (ARNr o proteínas ribosómicas) o reducción de la acumulación (por impermeabilidad o achique). El hecho de que ciertas posiciones en el ARNr participen en el enlace de antibióticos pertenecientes a familias distintas explica que las bacterias hayan adquirido mecanismos que pueden dar lugar a resistencia cruzada.

Palabras clave
Ácido fusídico – Aminoglucósido – ARNr 16S – ARNr 23S – Fenicol – Macrólido – Ortosomicina – Oxazolidinona – Pleuromutilina – Proteína ribosómica – Ribosoma – Síntesis proteínica – Tetraciclina.

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