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The Mechanisms of Resistance to Macrolide Antibiotics - An Overview

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ABSTRACT: Macrolides are among the most significant antibiotics in medical care.Macrolide resistance mechanisms can be target-based, with a mutation in ribosomal protein L4 or L22 or a change in a 23S ribosomal RNA (rRNA) residue impacting the ribosome's interaction with the antibiotic. Phosphorylation of the 20-hydroxyl of the amino sugar at position C5 by phosphotransferases and hydrolysis of the macrocyclic lactone by esterases are two drug-inactivating mechanisms. Because cells are less fit when these genes, particularly the rRNAmethyltransferases, are strongly stimulated or constitutively expressed, they are controlled by either translation or transcription attenuation. The mechanism of action of macrolides is skillfully linked to the activation of gene expression, with antibiotic-bound ribosomes halted at certain sections of nascent polypeptides promoting transcription or translation of downstream sequences.

KERWORDS: Macrolide Antibiotics, Resistances ,erm, Efflux, Inactivation.

I. INTRODUCTION:

MACROLIDE ANTIBIOTICS:

Macrolides are a class of clinically relevant antibiotics that are used to treat infections caused by Gram-positive bacteria like Staphylococcus aureus, Streptococcus pneumoniae, and Streptococcus pyogenes.[1]Macrolides are enormous lactone rings with 14-, 15-, or 16 members and one or more sugar moieties, usually desosamine and cladinose.[2]The basic behaviour of macrolides is extended by the introduction of another sugar moiety containing a dimethylamine group. Antibiotics are used to treat a variety of issues, including allergic responses, gastrointestinal distress, sluggish bactericidal action, and hepatotoxic consequences.[3,4]Macrolide antibiotics are classified by their generation. Erythromycin, carbomycin, spiramycin, oleandomycin, rosaramycin, and josamycin are among the first generation antibiotics. Macrolides of the second, more recent generation are semi-synthetic natural product derivatives. The usage of previous macrolides has been linked to a number of side effects, which has led to a withdrawal from these medications and the development of side-effect-free' macrolides like clarithromycin and azithromycin. Clartyromycin, azithromycin, midecamycin, dirythromycin, roxithromycin, flurithromycin, azithromycin, miokamycin, and rokitamycin are examples of second-generation macrolides.[5,6]Macrolide antibiotics have a wide range of activity. Both Gram-positive and Gram-negative bacteria are susceptible to them.The action spectrum of macrolides varies slightly, but the range is often similar. The drug's chemical structure influences pharmacokinetic characteristics, resulting in these discrepancies.[1]

Classification Of Macrolide Antibiotics:

Clinically relevant macrolide antibiotics are divided into three groups based on the number of atoms in the lactone ring: 14-membered, 15-membered, and 16-membered antibiotics.[7]

14-membered macrolide antibiotics:

Erythromycin,
clarithromycin,
roxithromycin are 14-membered macrolide antibiotics.[7]

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Erythromycin: The first macrolide antibiotic is erythromycin. A strain of Streptomyces erythreus was identified from a soil sample by some Filipino scientists in 1949. It is available in the form of Tablets, capsules, oral suspensions, ocular solutions, ointments, gels, and injections . With a melting point of 191°C and a dissociation constant pKa= 8.9. It is a white or slightly yellow crystal or powder.[8]

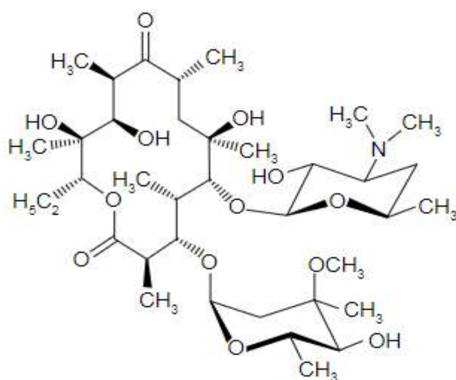

FIGURE:1Structure Of Erythromycin[9]

Clarithromycin: Clarithromycin was invented in 1970 by researchers at Taisho Pharmaceutical, a Japanese pharmaceutical business (6-O-methyl erythromycin). Clarithromycin was patented by Taisho in 1980. It's available in tablet, oral suspension, gel, and lotion form. It's a white crystalline solid with a melting point of 217–220°C and a pKa = 8.99 dissociation constant. It is mildly soluble in acetone and ethanol, methanol, and acetonitrile.[8]

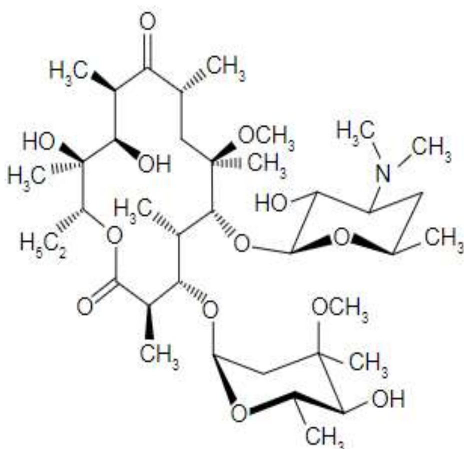

FIGURE:2Structure Of Clarithromycin[10]

Roxithromycin: Roxithromycin is a macrolide antibiotic that is semi-synthetic. Roxithromycin was first introduced in 1987 by Hoechst Uclaf, a German pharmaceutical company. Tablets and oral suspensions are available. It's made from erythromycin with a side chain of N-oxime linked to the lactone ring. It's a white solid with a melting point of 111 degrees Celsius. Ethanol, methanol, acetonitrile, and acetone are all soluble in it.[11]

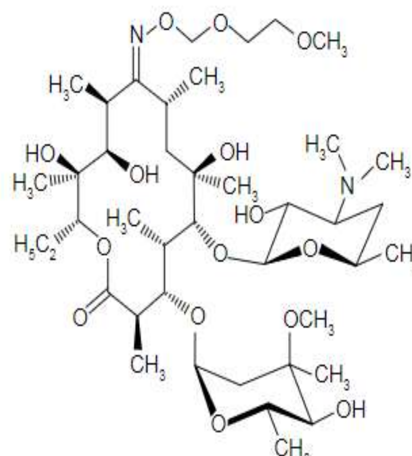

FIGURE:3Structure Of Roxithromycin[12]

15-membered macrolide antibiotics.

Azithromycin: Pliva, a Croatian pharmaceutical firm, discovered azithromycin in 1980. It is one of the most effective antibiotics. It is generated from erythromycin and has a 15-membered lactone ring due to the inclusion of a methyl-substituted nitrogen atom. It is available in tablet, oral suspension, and injectable form. It's a white solid with a melting point of 113–115°C and a pKa = 8.74 dissociation constant. Ethanol, methanol, acetonitrile, and acetone are all soluble in it.[13]

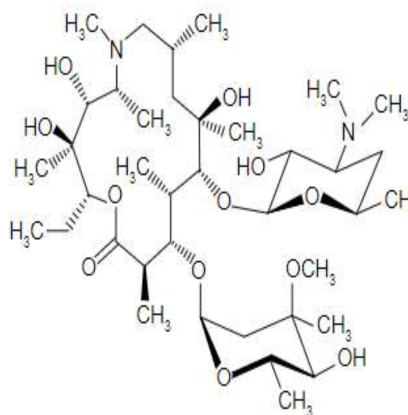

FIGURE:4Structure Of Azithromycin[13]

16-membered macrolide antibiotics.

Josamycin: Josamycin is produced by Streptomyces narbonensis var. josamyceticus strains. The melting temperature of this yellowish crystalline powder is 130–133°C. It's available in tablet form and as a dry syrup. Josamycin, unlike the 14- and 15-membered macrolide antibiotics, is not widely utilised.[14]

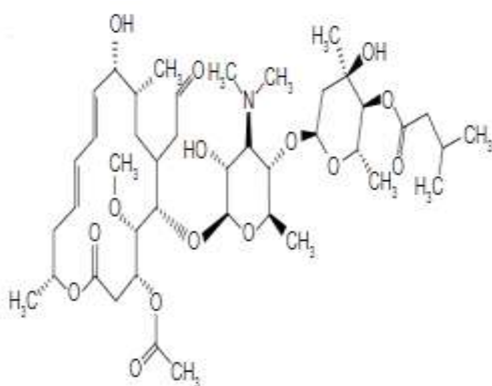

FIGURE:5Structure Of Josamycin[15]

MACROLIDE MECHANISM OF ACTION:

By binding to the 23S rRNA in the large ribosomal subunit (50S) downstream of the peptidyltransferase centre (PTC), the catalytic site for peptide bond production, macrolides suppress bacterial protein synthesis.[16,17,18]Macrolides/ketolides bind right above the constriction caused by prolonged loops of ribosomal proteins L4 and L22 at the entrance of the peptide exit tunnel (PET), further limiting the PET's effective diameter.[19,20] The 20 hydroxyl of desosamine sugar at C5 forms a critical hydrogen bond with the N1 atom of A2058, and mutation or methylation of the N6 exocyclic amine at this position results in macrolide resistance.[21]Macrolides were assumed to inhibit protein synthesis by sterically inhibiting nascent peptides as they passed through the PET until recently. Despite the constriction created by the L4 and L22 loops, as well as the bound macrolide, there is still enough room in the PET for nascent, unfolded peptides to effectively navigate the tunnel.[22,23]

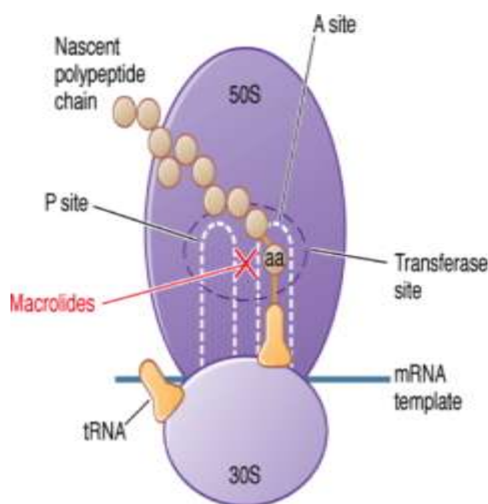

FIGURE:6 Mechanism of Action of Protein synthesis inhibitor (Macrolides)[24]

MECHANISMS OF RESISTANCE TO MACROLIDE ANTIBIOTICS:

Reduced drug binding affinity, caused by changes in either the bacterial ribosome or the antibiotic molecule, and efflux of macrolides from the bacterial cell, caused by changes in membrane permeability or efflux pump expression, are the two most prevalent resistance mechanisms in bacterial pathogens.[25]Drug-inactivating processes include phosphorylation of the 20-hydroxyl of the sugar by phosphotransferases and hydrolysis of the macrocyclic lactone by esterases, and ribosome modification mechanisms include either ribosomal 23S rRNA or large ribosomal subunit proteins.[26]

Mechanisms Of Acquired Macrolide Efflux:

Mef family:

Mef pumps are members of the major facilitator superfamily and are made up of 12 transmembrane domains connected by hydrophilic loops.[27]Mef pumps act as antiporters, exchanging a proton for the bound macrolide.[28]Grampositive bacteria contain mef genes, but certain Gram negative bacteria have been shown to have them as well.[29]Mef(A) and mef(B) are the two primary subclasses (E). Despite the fact that they share more than 80% homology, they are carried on separate genetic elements. Both genes provide resistance to 14- and 15-membered macrolides, lincosamides, and streptogramins B, but not to 16-membered macrolides, lincosamides, or streptogramins B, resulting in the 'M phenotype' but not the 'MLSB phenotype.' Mef(E), like the msr(A) family of genes from Staphylococcus

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aureus, has an adjacent ATP-binding cassette-type transporter gene called msr(D).In S. pneumoniae, co-expression of Msr (D) and Mef(E) is essential for high-level macrolide resistance, and both proteins work together to promote macrolide resistance in E. coli. Transcription attenuation regulatesmef genes, with anti-attenuation of transcription in the presence of inducing macrolides causing induction of the mef(E)/msr(D) operon.[30] However, there is evidence that a second regulatory mechanism with a leader peptide encoded upstream of mef(E) exists.[31]

Msr family:

By binding to and chasing the bound drug from the ribosome, these proteins displace macrolide antibiotics from the ribosome, providing ribosome protection.[32]Types A, C, D, and E are the four classes of Msr proteins, each featuring an ATP binding motif and sequence homology with the ATP-binding superfamily.[33] The Msr family confers resistance to macrolides with 14 and 15 members, as well as a low level of resistance to ketolides. Staphylococcus epidermidis, Staphylococcus xylosus, Staphylococcus aureus, Enterococcus, Streptococcus, Pseudomonas, and Corynebacterium all have msr genes linked to macrolide resistance.[34,35,36] The Msr family was assumed to give macrolide resistance by serving as efflux pumps for a long time. Tet(M) and Tet(O) are paralogs of the translational GTPase EF-G and remove tetracycline from the ribosome in a GTP hydrolysis-dependent manner, resulting in tetracycline (not macrolide) resistance.[37]

RIBOSOMAL MODIFICATIONS:

Mutations in 23S rRNA:

Because of nucleotide alterations in either domain Vor helix 35 in domain II of 23S rRNA or ribosomal proteins L4 or L22, mutants resistant to one or more of the MLSB antibiotics give genetic evidence that these antibiotics interact with the ribosome.[38] Macrolides primarily interact with the 23S rRNA nucleotides A2058 and A2059, and mutations in these nucleotides have been found in many macrolide-resistant bacterial strains, mostly in pathogens (Mycobacterium, Brachyspira, Helicobacter, Treponema) that have only one or two copies of the rrl gene, which codes for 23S rRNA.Mutations in these positions, as well as G2057 in combination with A2059 and C2611, have been found in clinical isolates and laboratory mutants of S. pneumoniae, at A2058 and C2611 in clinical isolates of Streptococcus pyogenes, and at A2058, A2059, or both A2059 and G2160 in clinical isolates of Haemophilusinfluenzae. In all species, mutations at A2058 and A2059 are the most common and exhibit a robust phenotype, conferring macrolide–lincosamide–streptogramin B-ketolide (MLSBK) resistance in the majority of isolates.[39,40]

Ribosomal protein mutations:

Erythromycin resistance and telithromycin susceptibility can be conferred by mutations in the genes encoding the ribosomal proteins L4 and L22. In addition to E. coli laboratory isolates, ribosomal protein mutations that confer macrolide resistance have been found in S. pneumoniae, S. pyogenes, St. aureus, H. influenzae, and Mycoplasma genitalium clinical isolates.[41,42]Changes in a highly conserved S. pneumoniae L4 sequence (63KPWRQKGTGRAR74) resulted in lower sensitivity to macrolides or ketolides (a 500-fold increase to a telithromycin MIC of 3.12 mg•mL 1 for one variation), as well as a decrease in fitness.[39]Although the MICs in S. pneumoniae were not larger than 1 mg•L 1, mutations encoding amino acid alterations in the C-terminal region of ribosomal protein L22 (e.g. G95D, P99Q, A93E, P91S, G83E, A101P, and 109RTAHIT114 tandem duplication) resulted in lower susceptibility to macrolides and ketolides. When 23S rRNA methylation/mutations are coupled with ribosomal protein mutations in S. pneumoniae, resistance to telithromycin increases dramatically. Because all prior protein mutation locations are somewhat distal from the macrolide binding pocket (9–10), it was suggested that resistance could be generated by induction of structural alterations in the rRNA nucleotides that spread to the antibiotic binding pocket.[43]

erm Genes:

Erm genes encode rRNAmethyltransferases that add one or two methyl groups to the exocyclic amino group of A2058 found in the PET of 23S rRNA, which is a key and common mechanism of resistance to macrolide antibiotics.[44] Resistance to two further kinds of antibiotics, lincosamides and streptogramin B, is conferred in addition to resistance to 14-, 15-, and 16-membered macrolides and ketolides, giving the host the MLSBK phenotype. As of January 2016, there were 38 erm genes known.The most frequent erm gene is erm(B) (36 genera), followed by erm(C) (32 genera), erm(F) (25 genera), erm(X) (15 genera), erm(V) (11 genera), erm(A) (nine genera), erm(G) and erm(E) (seven genera each), erm(Q) (six genera), erm(T) (four genera), erm (two genera

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each). Only one genus contains the remaining 25erm genes. Sixteen (46%) of the erm genes are unique to environmental bacteria (erm(H), erm(I), erm(N), erm(O), erm(R), erm(S), erm(U), erm(W), erm(Z), erm(30), erm(31), erm(32), erm(34), erm(36), erm(37), erm(38).[45,46]

Inducible or Constitutive MLSB Phenotype:

Antibiotics can either inducibly or constitutively express erm genes, depending on the nature of the leader sequences upstream of the translational start site; examples include erm(A), erm(B), erm(C), and erm(D) (D).[47] Leader sequences form at least two stem and loop structures upstream of the translational start site for inducible erm genes, one of which sequesters the ribosome start site for the resistance gene and the other of which overlaps ORFs for one (erm(C), erm(B), erm(D)) or two (erm(A)) short peptides. The upstream leader sequence and attendant peptide are produced in the absence of an inducing antibiotic, but the erm gene is not synthesised due to sequestration of its ribosome-binding site. A macrolide-stalling motif in the nascent leader peptide is encountered in the macrolide-bound ribosome, and translation is halted. The stalled ribosome causes an alternative messenger RNA (mRNA) secondary structure to develop, exposing the erm gene's ribosome-binding site and making it available for translation by a ribosome that is not bound by erythromycin. Both the inducer (small chemical) and the leader peptide are required for translation to be stopped.[48,49]Despite the extremely conserved nature of the genes themselves, the regulatory leader regions of the mRNA transcripts for the various classes of erm genes are widely variable, allowing for a diversity of phenotypes relating to antibiotic induction.Although most erm genes are induced by 14- or 15-membered macrolides rather than 16-membered macrolides or ketolides, inducible resistance in Streptomyces spp. is the most diverse, with lincomycin and streptogramin B inducing N6 dimethylation of 23S rRNA and an MLSB-resistant phenotype in corresponding producers.[50]

Constitutive MLSB resistance can be conferred by a variety of mutations in the leader sequence, including deletions of the entire attenuator region for erm(C) in clinical isolates of S. epidermidis and S. aureus, and for erm(B) in E. faecalis, S. agalactiae, and S. pneumoniae, as well as tandem duplications in the attenuator of erm(C) of Telithromycin resistance was found in constitutive erm(B)-containing pneumococcal isolates with a greater percentage of 23S rRNA methylation.[51,52]

cis-Acting Peptides:

Macrolides can disassociate from the ribosome when a pentapeptide encoded in E. coli 23S rRNA is translated, imparting macrolide resistance.[53] Using a random-library technique, further cis-acting peptides (resistance granted solely to the ribosome on which the peptide is generated) have been found, yielding the consensus sequence fMet. Other consensus peptides specific for distinct macrolides (e.g., oleandomycin, ketolides, 15-membered macrolides) were also found, demonstrating the PET's ability to discern modest alterations in antibiotic/nascent peptide interactions.[54]The affinity of the macrolide/ketolide for its binding site is diminished when crucial amino acids are produced in specific short peptides, but removal of the antibiotic from the ribosome is most likely when the pentapeptide is released from the peptidyl-tRNA by class I release factor.[55]

MACROLIDE INACTIVATION:

Modification by macrolide esterases:

In 1984, the first erythromycin esterase was discovered in a macrolide-resistant E. coli strain.[56]TheereA gene was cloned to produce a 406-amino-acid protein with a predicted mass of 44.8 kDa. Another orthologue, ereB, was cloned from another E. coli isolate after that.[57] Both Ere(A) and Ere(B) hydrolyze the lactone ring in 14-membered macrolides; nevertheless, the two enzymes have only a 25% protein sequence similarity. The catalytic mechanisms of the 'erythromycin esterase superfamily' enzymes were compared using a genomic enzymology approach. Esterases only inactivate 14- and 15-membered macrolides, whereas ketolides and 16-membered macrolides, such as josamycin, midecamycin, rosaramycin, and spiramycin, are not.[58]

Phosphotransferases:

Macrolide phosphotransferases are macrolide-inactivating enzymes found in Gram-negative and Gram-positive bacteria, and they belong to the same family as aminoglycoside and macrolide protein kinases, according to in silico study.[59] Macrolide phosphotransferases were originally purified from macrolide resistant E. coli, and this mechanism was quickly found to be common in clinical isolates of E. coli Tf481A in Japan. Macrolide 20-phosphotransferases, which are commonly found on mobile genetic elements, are intracellular enzymes that transfer the -phosphate of nucleotide triphosphate to the

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desosamine 20-OH group of 14-, 15-, and 16-membered ring macrolide antibiotics, disrupting the key interaction of macrolides with A2058.[60]Mphs are classified into two groups based on differences in primary sequence and substrate specificity, and their structures in complexes with numerous macrolides have been determined to atomic resolution. Mph enzyme genes are typically found on mobile genetic elements that also contain additional macrolide resistance genes as well as genes giving resistance to other antibiotic classes. mph (G), the most recently discovered macrolide phosphotransferase, was discovered in Vibrio spp. and photobacteria in fish farm seawater.[61]

II. CONCLUSION:

Macrolides are capable of controlling inflammation and have a wide range of biological actions. The accumulation of macrolides within cells raises the possibility that they may interact with receptors or carriers that control the actions of immune cells. Specifically, ribosomal methylation by the gene product expressed by erm (B) and macrolide efflux by a two-component efflux pump encoded by mef (E) on the transformable genetic element mega are responsible for S. pneumonia's macrolid resistance. The complexity of the resistance phenotypes reflects the diversity of mechanisms that give resistance to macrolides; however, the methylase and efflux genes are the most clinically significant and widespread determinants in gram-positive organisms.

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