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Mechanisms of Antibiotics Resistance in Bacteria

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ABSTRACT
The resistance is determining a growing hug issue in health fields worldwide, where the bacterial cells possessed the ability to resist the old antibiotics as well as the newly discovered antibiotics through several capabilities and mechanisms, including the natural, acquired and cross ones, this paper will highlight most of the antibiotics and the mechanics of resistance.
Keywords: Resistance, Antibiotics, Bacteria, QRDRs, Efflux pumps

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INTRODUCTION

Bacterial resistance is the capability of bacterial cells to prevent antibiotic bacteriostatic or bactericidal effects [1]. The excessive and unintended usage of antibiotics contributes to resistance development in bacteria [2]. Because of the extensive antibiotics' uptake, the evolvement of microorganisms resistant with the time and problems have arisen with these resistant microorganisms for the treatment of certain infections [3]. Nowadays, resistance is determining as a big issue in the path of new drug synthesis, developing antibiotic resistance is a major public health problem worldwide [4].

The four principal forms of antibiotic resistance evolve as

1- Natural resistance (Intrinsic, Structural)

In this type of resistance, the usage of antibiotics is not associated with the resistance but it caused by the bacteria's structural properties [5]. This occurs as a result of intrinsic resistance, or microorganism which doesn't follow the target antibiotic structure, or antibiotics which due to its characteristics do not encounter its target [6]. Gram-negative bacteria and vancomycin, for example, vancomycin antibiotics does not move through the uter membrane so that these Gram-negative bacteria are naturally insusceptible to vancomycin [7].

Likewise, L-form bacteria that are cell wall-less types of the bacteria, such a *Ureaplasma* and *Mycoplasma Mycoplasma* that are naturally owning beta-lactam antibiotics resistance [8].

2. Acquired resistance

Regardless of resistance development due to alteration in the genetic features of bacteria, an acquired because it is not affected by the antibiotics it was previously susceptible to it [9]. This form of resistance comes from the main chromosome or extra chromosome structures (plasmids, transposons, etc.) [10].

Chromosomal resistance results from mutations that change randomly bacterial chromosome, these mutations can occur by certain physical and chemical factors [11].

This may be due to changes in the composition of bacterial cells, so that may be decreased bacterial drug permeability, or maybe changes to the drug's target in the cell [12]. Streptomycin, aminoglycosides, erythromycin, and lincomycin can develop resistance to these forms [13].

Extrachromosomal resistance relies on extrachromosomal genetic materials that can be transmitted via plasmids, transposons, and integrons [14]. Plasmids are segments of DNA that can replicate independently of chromosomal DNA [15]. A plasmid is typically responsible for the development of antibiotic inactive enzymes [16].

There are main forms of holding genetic material (resistance genes and plasmids) from bacterial cells, this form are transduction, transformation, conjugation, and mechanism of transposition [17].

The genes with antibiotic resistance on the chromosome or plasmid are intertwined and are situated at the beginning with different integration groups, or integrons. Recombination is very normal in integrons [18].

3. Cross-resistance

It is mean the resistance to a specific antibiotic by specific microorganisms, that work with the identical or related mechanisms and that are also resistant to other antibiotics [19]. This is generally seen when antibiotics have common structures: such as resistance to erythromycin,neomycin-kanamycin, or resistance to cephalosporins and penicillins [20].

However, cross-resistance can some times be seen in a completely distinct group of drugs as well, like a cross-resistance that exists amongst erythromycin-lincomycin, this resistance might be the chromosomal origin or not [21].

4. Multi-drug and other types of resistance

Multidrug-resistant species are typically pathogens that have been resistant to their antibiotics, this ensures that the bacteria will no longer be eliminated or regulated by a single drug [22]. Inappropriate utilization of drugs "antibiotics" for treatment culminated in the introduction of multidrug-resistant pathogenic bacteria [23]. Either of the two mechanisms can induce multidrug resistance in bacteria [24].

Firstly, these bacteria will acquire several genes, each coding for specific drug resistance, this form of resistance usually exists on R-plasmids [25].

Secondly, the form of multidrug resistance may also occur by enhanced gene expression encoding for efflux pumps, enzymatic inactivation for antibiotics, changes in target structure, and others [26].

If the bacterial strains are not susceptible to three or more antimicrobial types, they are called multidrug-resistant (MDR) bacteria. If the species, resistant to all but one or two classes of antibiotics, are deemed highly resistant to medicines, whether the species resistant to all usable antibiotics are known as pan-drug resistant [27,28].

For example, *Acinetobacter* species with multidrug resistance (MDR) can be identified as the bacteria that having the resistant ability to at least three groups of antibiotics classes, for example for all penicillin and cephalosporin, aminoglycosides and quinolones groups [29].

Extensive *Acinetobacter* spp., drug-resistant (XDR), isolate resistant to the three types of antibiotics classes mentioned above in (MDR), and even carbapenem-resistant, *Acinetobacter* spp. , Pandrug resistant, or pan-resistant (PDR), these bacteria can be going to be the XDR as well as polymyxin-resistant and tigecycline resistance [30,31].

Mechanisms of Antibiotics Resistance

A-The modifications

Modifications that happen in the drug-related receptor and the location of the target regions of the relation with the antibiotics are distinct, these can be complex enzymes and ribosomes [32]. The most frequently identified resistance consistent with variations in the ribosomal target is in macrolide antibiotics [33]. The most popular examples here are the evolvement of penicillin resistance due to the mutations of penicillin-binding proteins beta-lactamase enzymes in *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Neisseria meningitides*, and *Enterococcus faecium* strains [34].

B. Enzymatic inactivation of antibiotics

Most of the bacteria synthesize antibiotic degrading enzymes, the enzymatic inactivation mechanism is one of the most important antibiotics resistance mechanisms [35]. In this group, beta-lactamases, aminoglycosidase, chloramphenicol, and erythromycin modifying enzymes are the most popular examples [36].

C. Reduction of the inner and outer membrane permeability

This mechanism results from changes in the permeability of the internal and external membrane so that decreased drug uptake into the cell or rapidly ejected from the pump systems [37]. Due to a decrease in membrane permeability as a result of porin mutations that may occur in proteins of resistant strains for example; a mutation in specific porins called OprD can cause resistance to carbapenem in *Pseudomonas aeruginosa* strain [38]. Reduction in outer membrane permeability can play an important role in quinolone resistance and aminoglycoside resistance [39].

D. Active Pumps System

Resistance develops most commonly in the tetracycline group of antibiotics via the active pump systems [40]. With an energy-dependent active pumping system, tetracyclines are thrown out and cannot concentrate within the cell[41]. This mechanism of resistance is in plasmid and chrom osomal control. Active pumping systems for example are effective in resisting quinolones, 14-membered macrolides, chloramphenicol and beta-lactams [42].

E. Using an alternative metabolic pathway

Unlike some of the target alterations in bacteria, the latest drug-susceptible pathway eliminates the need for objective development [43]. Bacteria can prepare folic acid from the environment, rather than synthesizing folic acid so that it becomes resistant among sulfonamide and trimethoprim [44].

Resistance by Antibiotics group Mechanisms

A. Beta-lactams Resistance

Antibiotics of beta-lactam are a wide class of antibiotics, including penicillins, cephalosporins, monobactams, and carbapenems [45]. Synthesis of beta-lactamase enzymes is the most common resistance mechanism here [46].

1- Beta-lactamase Enzymes

At the molecular level, there are 4 groups (A, B, C, D)of beta-lactamase enzymes [47]. Beta-lactamases A, C, and D that deferent from B-class that function cool ester enzymes mediated, while the latest was need zinc ion as metalloenzyme [48].

Beta-lactamases Class A

These resistances occur in both Gram-positive and Gram-negative bacteria and mostly mediated by plasmid or transposon. Capable usually of being inducible [48]. This group includes the gram-negative bacteria TEM, SHV, ESBL. ESBL primarily occurs in *E. coli* and *Klebsiella pneumoniae* [49].

Beta-lactamases Class B

Bacteroides fragilis, observable species of *Aeromonas* and *Legionella*, enzymes that hydrolyze carbapenems, penicillin, and cephalosporins [50].

Beta-lactamases Class C

Generally seen in Gram-negative bacteria and chromosome-localized (Group I, AmpC, etc.) [51]. This resistance mechanism is not inhibited by clavulanic acid and has an inducible characteristic so produced high levels the presence of beta-lactam antibiotics [52]. Often known as Inducible Beta-Lactamases (IBL), they found in *Enterobacter cloacae, Citrobacter freundii, Serratia marce scens, and P. aeruginosa* [53].

Beta-lactamases Class D

These enzymes are induced by beta-lactamases antibiotics and produced in Gram-positive *cocci such as Staphylococcus* aureus so that degrade Oxacillin [53].

2. Modifications in Penicillin-Binding Proteins (PBP)

Penicillin-binding proteins (PBP) in peptidoglycan synthesis in the bac responsible for the Antibiotic target of beta-lactam, Carboxypeptidase PBPs, and the enzymes of

transpeptidase PBP is the most common in gram-positive bacteria, due to changes in it, resistance results in [54]. Methicillin-resistant *S. aureus* (MRSA) is willing to take responsibility for methicillin resistance in strains, mecA gene, this gene results in PBP-2a synthesis enhancing beta-lactam antibiotic resistance [55]. The modifications in *S. pneumoniae* in PBP 2b are responsible for the resistance to penicillin and cephalosporin [56].

3. Modifications in Proteins of the membrane

Change in the porin channels in gram-negative bacteria, for example, *P. aeruginosa* with a devoted channel protein registered in OprD may evolve carbapenem resistance [57]. Antibiotic accumulation can be prevented in the active pump systems cell. Consequently, the group of beta-lactams, tetracyclines, chloramphenicol, and quinolones can lead to resistance [58].

B. Antibiotics Resistance of Aminoglycoside Group

1. Aminoglycosides Modifying Enzymes

The most important mechanism for the emergence of resistance to aminoglycosides in aerobic gram-negative bacteria is enzymatic inactivation. Enzyme modifying has a major role in resistance to aminoglycosides [59]. These enzymes are often of plasmid or transposon origin, there are acetyltransferase and phosphotransferase in this group [60]. Modified enzymes are responsible for the high extent of gentamicin resistance in enterococci [61].

2. Ribosomal target Modifications

This approach is crucial in Streptomycin resistance, the target of streptomycin is not connected to the ribosomal 30S subunit due to mutations in the ribosomal 30S, in enterococci, this kind of resistance to streptomycin is essential [62].

C. The resistance of Tetracyclines

1. Prevention of the absorption of drugs into cells and active pump systems

Reduction of membrane permeability resulting from spontaneous chromosome mutations in bacteria as a result of resistance development to prevent drug uptake [63]. The organisms also can develop Tetracyclines resistance depending on active pump systems [64].

2. Protection of Ribosome

The second significant mechanism which leads to tetracycline resistance [65]. With tetM, tetO, tetQ, tetS genes inhibit drug activity by modifying a cytoplasmic ribosome that binds to the tetracycline [66]. These genes have been found in many genera like *Campylobacter*, *Mycoplasma*, *Ureaplasma*, and *Bacteroides*, for example. They are plasmid and chromosome origin [67].

D. The resistance of Macrolide, lincosamide, streptogramins (MLS)groups

Gram-negative bacteria are naturally resistant to MLS group antibiotics

1. Ribosomal Target Modification

This mechanism is most common in Gram-Positive bacteria, in the 50S ribosomal subunit, this is connected to the drug with the 23S of the ribosome in rRNA-specific methylation of an adenine molecule has structural change and reduces the drug's binding to ribosomal RNA. The resistance is of a structural or inducible type [68,69].

2. Inactivation of drug by Enzymatic activity

The bacterial cells having enzymes that play a critical role in resistance like Erythromycin and other Macrolides resistance [70].

E. The resistance of Chloramphenicol

The inactivation of the chloramphenicol acetyltransferase (CAT) by enzymes that acetylate the chloramphenicol antibiotic leads to resistance in bacteria produced by this enzyme [71]. Reduced drug uptake in certain bacteria especially gram-negative can also be responsible for chloramphenicol resistance [72].

F. The resistance of Quinolones

There are different mechanisms for quinolone resistance that including

1. Mutation modification of the target topoisomerase

Modifications in the target enzymes “topoisomerases” caused mainly by mutations that reduce the affinity of quinolones without compromising the enzyme function are the most common mechanism of acquired quinolone resistance and have already been reported in several bacterial species [73,74]. resistance-related mutations are clustered in discrete regions of the enzyme subunits, called regions determining quinolone resistance (QRDRs) [75].

2. A decreased intake of drugs by reduced permeability or active efflux

Increased resistance to quinolones in gram-negative bacteria due to variations in their outer membrane proteins so that they reduce the intake of drugs [76].

3. The target protection of topoisomerase with specific proteins

Target protection is provided by a family of small pentapeptide-repeat proteins, called Qnr proteins, which bind to the targets for topoisomerase and protect them from quinolone interaction [77]. A similar mechanism has developed in bacteria to protect topoisomerases from microcin, which are pentapeptide-repeat family proteins that are produced as a mechanism of biological competition by certain bacteria and can kill susceptible bacteria by inhibiting their topoisomerases [78].

4. Inactivation of the drug

The most recently identified mechanism of resistance to quinolones was inactivation by drug modification [79]. Acetylation is performed by a plasmid-encoded AAC enzyme variant which, has the ability to acetylate some quinolone molecules in addition to aminoglycosides and have unsubstituted secondary amines such as ciprofloxacin and norfloxacin [80].

G. Resistance of Rifampicin

The high-level resistance develops readily mainly due to chromosomal mutation in most bacteria so developed of stable changes that prevent binding in RNA polymerase [81]. Rifampicin should only be used in association with another antibacterial drug since the mutation risk is high. Rifampicin resistance is not transferable, and other antibacterials do not have cross-resistance [82,83].

H. Resistance of Sulfonamide and Trimethoprim

Sulfonamides are para-aminobenzoic acid analogs (PABA) and the dihydropteroate synthesis (DHPS)enzyme and trimethoprim dihydrofolate reductase (DHFR) metabolic pathways inhibiting tetrahydrofolic acid synthesis in bacteria [84,85]. Chromosomal and plasmid-mediated resistance to sulfonamides and trimethoprim [86]. Bacterial expression of the DHPS sulfonamides low-affinity plasmid comprising this case is the most commonly observed resistance to sulfonamide [87,88].

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CONFLICT OF INTEREST

None to declare.

ETHICAL CLEARANCE

All data was approved and carried out in accordance with approved guidelines.

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