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Mechanisms of Antimicrobial Resistance (AMR) in Bacteria

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Abstract

Antimicrobial resistance (AMR) is recognized as one of the major global health challenges and "ticking time bomb" of the 21st century. The resistance of bacteria to antibiotics hinders the efficiency of antibiotic use in the health care, and there is significant evidence to prove that the misuse of antibiotics will eventually result in the development of resistance. The clinical pipeline of new antimicrobials is dry, the last new class of antibiotic (daptomycin) approved in 2003 by the US FDA. This fact confirms that antimicrobial agents found on the market in the last 30 years are only associations or improvements of existing molecules.

Introduction

The struggle of mankind against infectious diseases is well known. The discovery of antibiotics led to optimism that infections can be controlled and prevented. Antimicrobial resistance happens when microbes like bacteria and fungi develop the ability to defeat the drugs designed to kill them. That means the germs are not killed and continue to grow. Resistant infections can be difficult, and sometimes impossible, to treat. Antimicrobial resistance is an urgent global public health threat, killing at least 1.27 million people worldwide and associated with nearly 5 million deaths in 2019 (Hofer *et al*., 2019).

What is an antimicrobial?

Any substance of natural, semisynthetic or synthetic origin that kills or inhibits the growth of microorganisms, such as bacteria, viruses, protozoa and fungi. Antibiotic is a substance that at a low concentration either inhibiting the bacterial growth or killing the bacteria.

Antibiotics classification and mechanism of action

Antibiotics work on selectively target specific killing and classify based on spectrum of activity and type of effect on bacteria. Depending on the range of bacterial species susceptible to these agents, antibiotics are classified as broad-spectrum, intermediate-spectrum, or narrow- spectrum. Bactericidal are those that kill target organisms whereas, Bacteriostatic inhibit or delay bacterial growth and replication. Different antibiotics have different modes of action (Figure 1), that is based on certain specific target sites within bacterial cells.

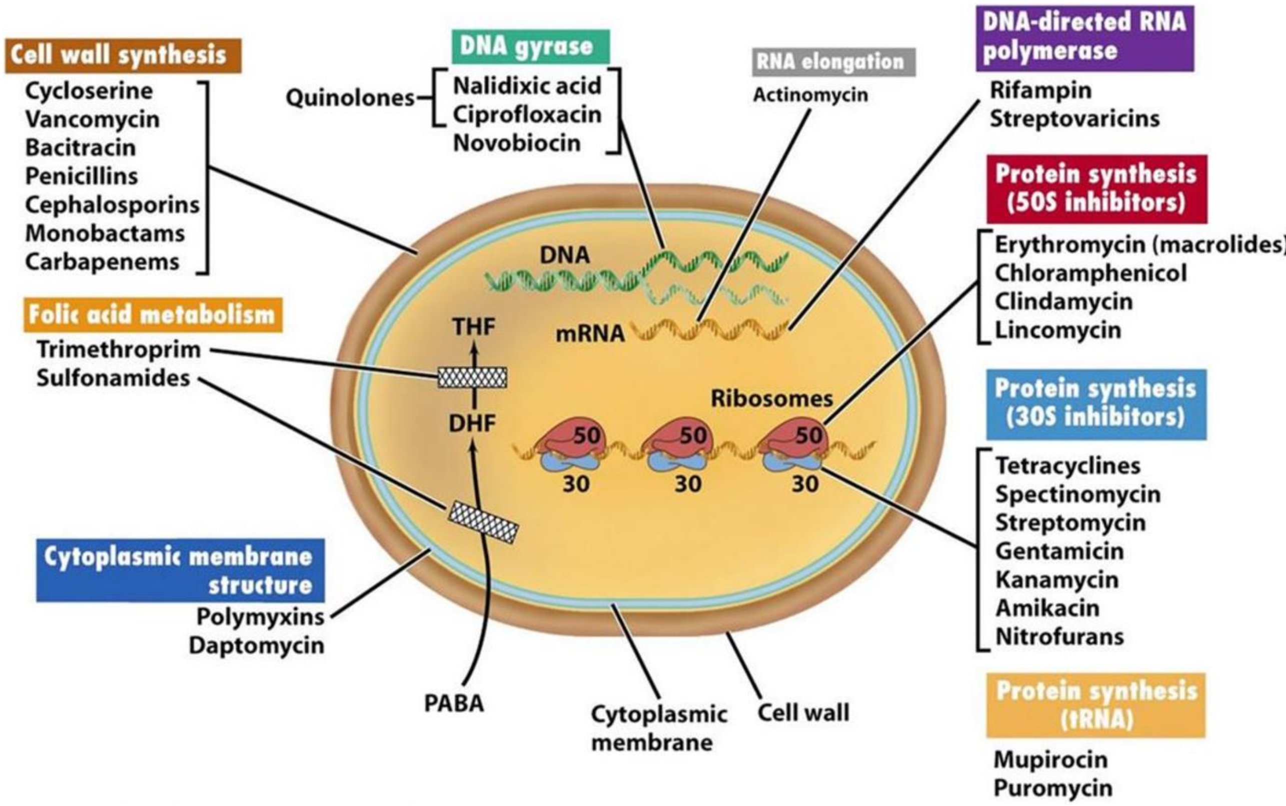

Figure 1: Bacterial target sites and mechanism of action of Antibiotics

(Source: Etebu & Arikekpar, 2016)

Antimicrobial resistance (AMR)

Antimicrobial resistance (AMR) defined as the ability of microorganisms to survive and be viable under the influence of antimicrobial agents. Several types of antimicrobial agents are present such as antibiotics, disinfectants, and food preservatives that can be used against microorganisms to reduce their capacity to grow, inhibit their multiplication or even kill them (Abushaheen *et al*., 2020).

Mechanisms of Antibiotic Resistance

To date, at least 17 different classes of antibiotics have been produced. Unfortunately, for each one of these classes at least one mechanism of resistance (and many times more than one) has developed over the years. In general, it can be said that bacterial resistance has its foundation at the genetic level. The expression of these genetic changes in the cell result in changes in one or more biological mechanisms of the affected bacteria and ultimately determine the specific type of resistance that the bacteria develop, resulting in a myriad of possible biological forms of resistance.

Genetic Mechanisms of Resistance

Resistance to antibiotics can be natural (intrinsic) or acquired and can be transmitted horizontally or vertically. The most common mechanisms of genetic transfer are conjugation, transformation and transduction (Christaki *et al*., 2020).

a. Conjugation

Conjugation is the most important and the most common mechanism of transmission of resistance in bacteria. This mechanism is normally mediated by plasmids (covalently close circular fragments of DNA) among bacteria via the formation of a temporary ‘‘pilus’’ (a hollow tubular structure) that forms between bacteria when they are next to each other and allowing the passage of these DNA fragments.

b. Transformation

Transformation takes place when there is direct passage of free DNA (also known as ‘‘naked DNA’’) from one cell to another. The ‘‘naked DNA’’ usually originates from other bacteria that have died and broken apart close to the receiving bacteria. The receiving bacteria then simply introduce the free DNA into their cytoplasm and incorporate it into their own DNA.

c. Transduction

Transduction is a third mechanism of genetic transfer and occurs via the use of a ‘‘vector’’, known as ‘‘bacteriophages’’ (phages). The phage containing the bacterial gene that codifies antibiotic resistance infects the new bacterial cell and introduces this genetic material into the receiving bacteria. Most time phage own DNA incorporates into bacteria and forcing bacteria to produce more copies of the infecting virus until the bacterial cell dies and liberates these new bacteriophages, which then go on to infect other cells.

Biological Mechanisms of Resistance

Whichever way a gene is transferred to a bacterium, the development of antibiotic resistance occurs when the gene is able to express itself and produce a tangible biological effect resulting in the loss of activity of the antibiotic (Figure 2).

a. Antibiotic destruction or antibiotic transformation

This destruction or transformation occurs when the bacteria produce one or more enzymes that chemically degrade or modify the antimicrobial making them inactive. This is a common mechanism of resistance for several antibiotics but especially beta-lactam antibiotics via the bacterial production of beta-lactamases enzymases (Murray *et al*., 2022).

b. Antibiotic active efflux

Antibiotic efflux pumps reduce the drug concentration without modification of the antibiotic itself. A decrease in the permeability of the outer membrane causes a decrease in influx of antimicrobial agents. Therefore, overexpression of pumps in bacteria causes resistance to antibiotics. Efflux was first described for tetracycline and macrolide antibiotics but is now common for many other antibiotics such as fluoroquinolones.

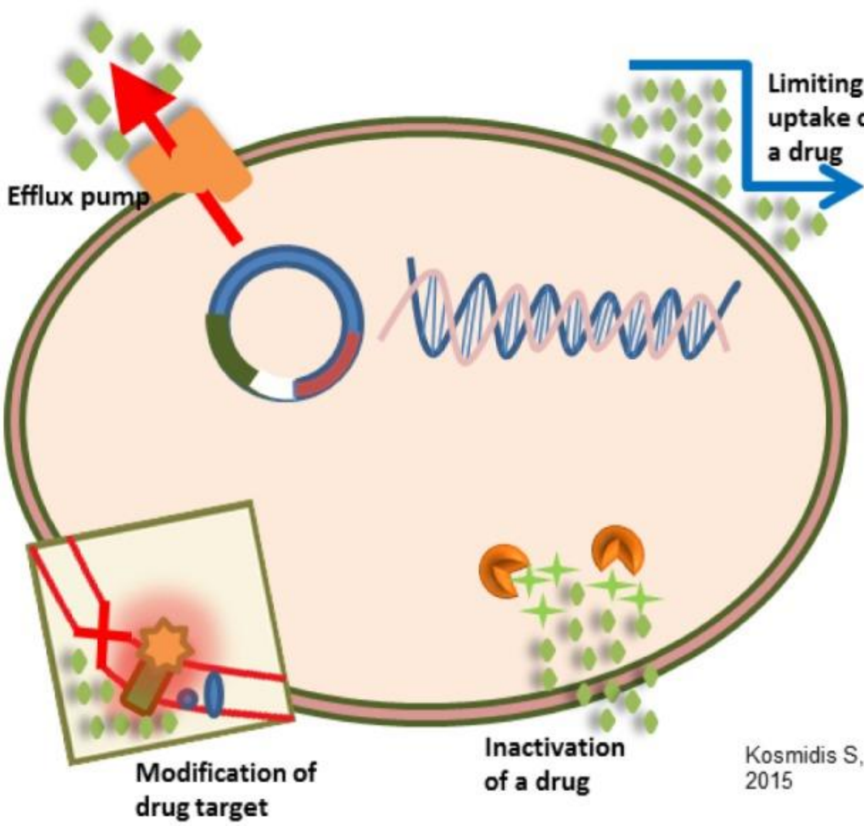

Figure 2. General antimicrobial resistance mechanisms

c. Receptor modification

Receptor modification occurs when the intracellular target or receptor of the antibiotic drug is altered by the bacteria, resulting in the lack of binding and consequently the lack of antibacterial effect. Examples includes modifications in the structural conformation of penicillin-binding proteins (PBPs) observed in penicillin resistance, ribosomal alterations that can render aminoglycosides, macrolides or tetracyclines inactive, and DNA-gyrase modifications resulting in resistance to fluoroquinolones (Reygaert, 2018).

Conclusions

Antibiotics have been a successful treatment method in preventing and treating microbial infections, and it has a key role in saving the lives of billions of people. There are many antibiotics which are currently in use in clinical field against which bacteria will continuously develop resistance by many different internal methods (such as mutations) and external methods (such as exchanging the resistant gene).

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