ANTIBIOTIC RESISTANCE – ONLY THE MOST ADAPTABLE TO CHANGES WILL SURVIVE

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ABSTRACT

Antibiotic resistance is a growing problem of the last decade. Excessive and incorrect use of antibiotics has led to a global public health crisis: the emergence of antibiotic-resistant strains that hamper the proper treatment of bacterial infections. Alarm Pathogens are the most dangerous microorganisms which are resistant to all of the available antibacterial drugs. The phenomenon of acquiring antibiotic resistance is mainly caused by horizontal gene transfer, however mutations of genetic information and vertical transfer of resistance genes are not insignificant. The main mechanisms that the microorganisms use in an unfavorable environment, enriched with an antibiotic, are the enzymatic hydrolysis of a molecule of a chemical compound, the enzymatic modification of the antibiotic molecule, the 'by-pass' reaction and efflux. The conscious use of one of the greatest medical inventions, which are antibiotics, gives a chance to reduce the population of alarm pathogens.

BACKGROUND

The ubiquitous microbial world is very diverse and abundant. It consists of bacteria, viruses, fungi, and protista. Although the majority of microorganisms play an important role in human life, some of them pose a serious threat, causing damage, disease and even death. In order to combat infectious diseases, antimicrobial agents (e.g. antiseptics, antibiotics or antifungals) have been developed to effectively eliminate or limit the growth of microorganisms [4]. The discovery of penicillin in 1928 by Alexander Fleming has made it possible to eliminate many onerous infectious diseases. Nowadays, those simple bacterial infections once again are becoming a threat to our health and life. The use of antibiotics has provoked evolutionary changes in microbial genome resulting in a development of resistance to the applied antimicrobial. Antibiotic resistance is a growing problem in last decade. We are witnessing the emergence of a new antibiotic-resistant strains. Alarm Pathogens (e.g. Pandrug Resistant bacteria, Extensively Drug Resistant bacteria, Multi Drug Resistant bacteria) are the most dangerous microorganisms which are resistant to all of the available antibacterial drugs. It is believed that the main reason of the antibiotic resistance crisis is the overuse and misuse of this pharmaceutics. Unfortunately, this issue does not only concern the medical world but also veterinary, agriculture and food industries [1, 2, 3].

GENETIC BASIS OF MICROBIAL RESISTANCE

Microorganisms have an extraordinary genetic plasticity that allows them to respond to a wide range of environmental threats, including the presence of antibiotics, that may threaten their existence. From an evolutionary point of view, bacteria use two main genetic defense strategies in the face of an antibiotic 'attack': mutations in a gene(s) and acquisition of a foreign DNA, containing antibiotic resistance genes, by means of a horizontal gene transfer (HGT) mechanism.

In the first case, bacterial cells, exposed to the antibiotic, develop a mutation in the genes that affect the activity of the drug. As a result, the antibiotic eliminates the sensitive part of the population and the newly emerging resistant mutants survive. Mutations that cause the antibiotic resistance are complex and are based on various mechanisms (described in the next chapter).

The most important mechanism for the bacteria to acquire an antibiotic resistance is the horizontal gene transfer (HGT). Bacteria can acquire external, foreign DNA in three ways: through transformation, transduction or conjugation.

Transformation is the simplest form of the HGT. This mechanism requires short fragments of naked DNA which are taken up by naturally transformable bacteria. Unfortunately, the transformation takes places only in specific environmental conditions such as altered cell growth, nutrient access, cell density or starvation that can lead to a development of a regulated physiological state of competence.

The second way of horizontal gene transfer is transduction which involves a transfer of DNA via bacteriophages.

Conjugation transfer is the most effective method of gene transfer between two bacterial cells. During the conjugation, mainly mobile genetic elements – MGEs (plasmids, transposons, and integrons) are transmitted. The genomic DNA is rarely the carrier of genetic information. The simplest and the most effective mechanism of accumulation of antibiotic resistance genes uses integrons, which are site-specific recombination systems capable of recruiting open reading frames [5, 6, 7].

MECHANISTIC BASIS OF ANTIMICROBIAL RESISTANCE

Over millions of years of evolution, bacteria have created many sophisticated drug resistance mechanisms to avoid death. The antibiotic resistance mechanisms are categorized as follows: I) modifications of the antimicrobial molecule, II) preventive measures to stop antibiotics from reaching their target (by decreasing penetration or actively extruding the antimicrobial compound), III) changes and/or bypass of the target sites, and IV) resistance due to a global cell adaptive processes [6].

I. One of the most effective bacterial strategies to eliminate the antibiotic from the environment is the production of enzymes that can modify the drug's molecule or destroy it completely. The enzymatic modification of the antibiotic molecule involves the incorporation of various chemical residues into its structure, which renders it inactive. Regardless of the biochemical nature of the reaction, it results in an increased minimal inhibition concentration (MIC) value of the bacteria. The main example of the enzymatic destruction of an antibiotic molecule is the hydrolysis of ß-lactam antibiotics by ß-lactamases [6, 8].
II. The second antibiotic resistance mechanism is the limitation of the cell membrane's permeability to prevent the antibiotic from reaching its intracellular target. This mechanism, in particular, affects hydrophilic antibiotics, such as ß-lactams, tetracyclines and some fluoroquinolones, which use porins to cross the outer membrane. Bacteria can also produce complex bacterial structures (efflux pumps) to remove toxic substances from within their cells [6].
III. Another strategy used by bacteria to defend against antibiotics is to avoid the effect of the antibiotic by interfering with its target site. Bacteria have evolved in two ways. One is to protect the target of the antibiotic molecule and second is to modify the target site to reduce its affinity towards the antimicrobial. Introducing modifications to the target site is one of the most popular mechanisms of antibiotic resistance in bacteria. These changes can take place in three ways: i) point mutations in the genes encoding the target site, ii) enzymatic alterations of the binding site and/or iii) replacement or bypass of the original target. Regardless of the

mechanism used, the final effect is always the same – a reduction of the drug's affinity to the target in the bacterial cell [6, 9].

IV. Through years of evolution, bacteria have developed many mechanisms to avoid the disruption of the fundamental cellular process such as cell wall synthesis and membrane homeostasis. The exact mechanism mediating in this phenomenon has not been fully elucidated [6, 9].

DISCUSSION AND CONCLUSIONS

The discovery of antibacterial substances and their use in clinical medicine is one of the greatest inventions of modern medicine. The creation of antibiotic resistance mechanisms is a natural adaptive bacterial response in line with the principles of Darwin's evolution. Despite the fact that having multiple resistance genes in plasmid DNA is beneficial for bacteria, in some cases, it may turn against them. The expression of resistance genes during bacterial growth in an antibiotic-free environment is a huge energy expense for the cell leading to its delayed growth. Resistant organisms are often at a disadvantage in terms of absolute growth rate in relation to sensitive organisms and therefore replacing the original bacterial cells in the population may not be so easy [10]. Bacteria are increasingly becoming exposed to more and more antibiotics, making the future strains of those bacteria stronger and more resistant. Shroeder and others have observed that the increase in virulence of bacteria occurs in parallel with the emergence of antibiotic resistance. The exchange, transfer, expression and regulation of virulence genes, and antibiotic resistance genes are further facilitated when both genetic elements are present on the same plasmid as well as when the bacteria are in a biofilm state [9].

Antibiotic resistance has, however, become one of the greatest threats to the public health of the 21st century as the identification of new compounds has become more difficult.

The conscious use of one of the greatest medical inventions, which are antibiotics, gives a chance to reduce the population of the alarm pathogens.

It is probably a long-lasting war with living organisms with great adaptability.

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ABBREVIATIONS

DNA – deoxyribonucleic acid,
HGT – horizontal gene transfer,
MGE – mobile genetic elements,
MIC – minimal inhibition concentration.

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