ANTIBIOTICS: THE SEARCH FOR NEW TARGETS

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Introduction. Antibiotics are the main group of drugs for the etiotropic treatment of infections. The multiple drug resistance of pathogens significantly reduces the effectiveness of therapy of infectious diseases. The traditional way to combat the problem is to develop new antibiotics that can destroy resistant mutants.

But at the modern time new antibiotics are structural analogues of existing chemical structural groups. The therapeutically significant resistance of bacteria to existing antibiotics has reached such a level that only the emergence of completely new antimicrobial agents can resolve the situation. Therefore, the search for new targets for antibiotics in a microbial cell is an urgent task of modern pharmacy.

Aim. Study of scientific literature on microbiological and pharmaceutical aspects of the search for new targets for antibiotics.

Materials and methods. Various information sources of Internet system, interlibrary loan and scientific library were used. An analysis of the ways of improving antibiotic therapy and creating fundamentally new groups of antibiotics.

Results and conclusions. The methods used in medicine for the development of bactericidal preparations are based on the identification of natural and synthetic compounds that affect actively dividing cells of microorganisms (staying in the logarithmic phase), as well as modifications of existing ones. For the production of analogues, natural base structures are used, such as 6-aminopenicillanic acid, the base of amoxicillin. Combined bactericidal agents, such as co-amoxiclav (complex of amoxicillin and clavulanic acid) are developed to suppress drug resistance.

The creation of derivatives of existing drugs is the most productive way of developing new antibacterial agents. New drugs are obtained and by artificial connection of components. To create new antibiotics, screening of compounds with enzymes or whole cells that are capable of disturbing the regulation of microbial RNA is also used.

The development of structural and functional genomics and the decoding of genomes of the main causative agents of human infectious diseases made it possible to identify potentially new targets in a microbial cell. It is known that the cell target can be a ligand-receptor, an enzyme or a certain pathway of metabolism. The main condition for using a new target of the pathogen is its absence in the human body, and this condition has proved very difficult to implement.

New targets for inhibitors in a bacterial cell can in principle be those that are

synthesized only in the infectious process and whose functions are realized only in vivo. Identification and study of such targets at the molecular level are possible with the help of such screening systems, where the genes encoding these targets are expressed in vitro. It is in vitro that infectious properties and the ability to survive in a human organism should be demonstrated. Scientists have developed a new technique for searching for new cellular targets - "In vivo gene expression technology" (IVET) with which it is possible to control precisely those genes that are selectively expressed in infection. Are induced in the pathogen only in vivo. In this way, the genes for the synthesis of some lipopolysaccharides expressed in vivo and not previously described, genes encoding the structure of enzymes that destroy the pathogen-toxic metabolites of the host, etc., were detected in this way.

Paradoxically, it is a fact: for twenty years of development in this direction, at the present time in medical practice there are no antimicrobial drugs created on the basis of genomics. This is primarily due to the fact that the defeat of the target does not always cause adequate bactericidal action, and the process of converting the resulting compound into a drug is quite complex and time-consuming. For example, with the help of genomics, deformylase was discovered, to suppress the action of which inhibitors that participated in clinical trials were developed. Deformylase is an enzyme that catalyzes the cleavage of formyl methionine from the newly synthesized polypeptide chain in prokaryotes. However, it was noted that the administration of these drugs causes bacterial mutations, and from further promotion of drugs refused.

Another example, GlaxoSmithKline used a genomic approach for 7 years. Over 300 genes were discovered during the research. However, none of the detected targets led to the development and market entry of a new antibacterial agent. While the failure of genomics in the development of antimicrobial drugs reduces the enthusiasm of pharmacists. It is still relevant to screen databases of natural compounds.

Combinatorial genetics will allow the creation of antibiotic-forming recombinant organisms. Another promising way of obtaining new antimicrobials is biologically active compounds of plant origin. But so far the most effective way of obtaining bactericidal medicines is to create new derivatives of existing antibiotics.

Potentially effective way of developing new antimicrobials is to develop antibacterial drugs based on bacteriophage genes. A promising example is lysine, which is an enzyme with hydrolase activity against the cell wall of Gram-positive pathogens. It does not cause bacterial resistance, does not neutralize antibodies; It is active against resting forms of bacteria and biofilms.

Thus, analysis of scientific literature has shown that data from genomics, bacteriophages and resting microorganisms are potential sources for the creation of new effective antimicrobial agents.