ISSN 0006-2979, Biochemistry (Moscow), 2020, Vol. 85, No. 11, pp. 1289-1291. © Pleiades Publishing, Ltd., 2020.
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Overcoming Antibiotic Resistance in Microorganisms: Molecular Mechanisms

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Received October 12, 2020
Revised October 12, 2020
Accepted October 12, 2020

Abstract—This issue of the Biochemistry (Moscow) journal presents reviews and experimental articles on the new strategies for solving the problem of antibiotic resistance and on the search for novel antimicrobial preparations using the methods of molecular biology, genetics, and nanotechnology. A wide variety of scientific approaches and successful (as a rule) research results give hope for overcoming microbial antibiotic resistance in the fight against infectious diseases.

DOI: 10.1134/S0006297920110012

Keywords: antimicrobial drugs, resistance, recombinant technologies, new inhibitors

INTRODUCTION

The emergence of stable antibiotics resistance of microorganisms is a global challenge of the XXI century [1]. The problem of overcoming drug resistance in the fight against infectious diseases attracts attention of researchers from different areas of science. Antibiotic resistance is associated with the fundamental features of microbial molecular biology. Biochemical processes responsible for the resistance to different antibiotics had emerged more than 2 billion years ago and have continuously evolved since then. The development of antibiotic resistance has been ensured by the interspecies competition between microorganisms, resulting in the emergence of microbes producing hundreds of different types of antibiotics, as well as the appearance of a large number of protective mechanisms [2]. Antibiotics target various metabolic processes and cell structures, such as components of the cell wall, peptidoglycan, genetic apparatus enzymes, ribosomes, and protein synthesis components. A complex of genes responsible for the resistance mechanisms was termed "resistome", and a complex of enzymes participating in antibiotic resistance – "enzystome" [3, 4]. These enzymes act as targets of antibacterial preparations, modify their structure, or change genetic targets of antibiotics in the cell. Antibiotics that affect protein synthesis and ribosome structure are the most widely used group of antimicrobial preparations, however, the resistance to them is due to the enzymatic modification of ribosomes [5, 6].

Approaches for overcoming antibiotic resistance include the development of various antimicrobial preparations with the employment of molecular biology, genetics, and nanotechnology techniques, the search for new bacterial targets, genome regulation, and the use of bacteriophages and antimicrobial peptides and proteins. A creative momentum in the search for novel antimicrobial preparations is associated with the detailed investigation of human and animal microbiomes, as well as studies of soil and water microbial communities [7].

These research directions are presented and discussed in the experimental and review articles of this issue of the Biochemistry (Moscow) journal.

OVERCOMING ANTIBIOTIC RESISTANCE IN MICROORGANISMS

Inhibitors of β-lactamases. Considering predominant use of β-lactam antibiotics, it is very important to preserve the potential of these compounds. The resistance to β-lactam antibiotics is based on the hydrolysis of the lactam ring by β-lactamases. Inhibitors of these enzymes administered together with the antibiotics allow to pre-

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serve the antimicrobial activity of β-lactams. The structures and the mechanisms of action of different generation inhibitors and the prospects for their application are presented in the review by Egorov et al. [8].

Peptidoglycan-recognizing proteins. Many other types of antimicrobial preparations target cell structures associated with the cell membranes. Among these preparations are peptidoglycan-recognizing proteins described in the review by Bobrovsky et al. [9]. These proteins, which are capable of binding bacterial peptidoglycan, are the innate immunity factors. The authors suggest an original technology for the human cell genome editing that could promote expression of genes encoding peptidoglycan-recognizing proteins.

Peptide antibiotics – lantipeptides. Gabibov et al. [10] described a group of lantipeptide antibiotics. Up to now, the use of peptide antibiotics (except vancomycin) has been limited due to their low specificity and instability, as well as due to manufacturing difficulties. The authors suggest a new approach for the production of a wide variety of peptide antibiotics with genetically altered primary structure with the use of microfluidic technology to screen for the biological activity of the produced antimicrobial peptides.

Methylation and antibiotics. Ribosomal functional centers are the popular targets of antibiotics in microorganisms. Methylation of nucleotide residues by methyltransferases is a mechanism of resistance to macrolides and other antibiotics. Methylation reactions in different ribosome centers providing resistance to different groups of antibiotics are described in the review by Dontsova et al. [11]. The authors also discussed genetic mechanisms involved in the synthesis of methyltransferases and their role in the evolution of antibiotic resistance.

Bacteriophages represent an old-new approach in the fight against multidrug-resistant bacteria. As viruses of bacteria, bacteriophages possess genetic mechanisms for overcoming the resistance. Unlike antibiotics that usually exhibit a broad-spectrum activity, bacteriophages are specific against particular infectious agents, which affects their large-scale production and application. The properties of bacteriophages can be changed by genetic engineering methods to expand their area of application. This topic is presented in the polemical review by Vlasov et al. on the medical use of bacteriophages [12].

Marine bacteria are a new source of antibacterial preparations. Numerous antimicrobial metabolites with varying structures, which often have no analogues, have been isolated from the extracts of marine bacteria. The studies of these antibiotics are reviewed in the article by Stonik et al. [13]. Many of these preparations are in different phases of pre-clinical and clinical trials.

New generation antibiotics. Different approaches for solving the problem of bacteria resistance are presented in the article by Shemyakin et al. [14], including the methods based on the use of small non-coding RNAs (sRNA) and CRISPR-Cas systems that play an important role in regulation of genetic processes in bacteria. Although at present these methods are at the experimental stage of development, they are considered as very important from the scientific point of view. The authors give special attention to the inhibitors of cellular processes and proteins, such as β-lactamases, efflux pumps, transmembrane transport, biofilms, virulence factors, and mechanisms of cell–cell communications. Some of these inhibitors have already found their practical application in medicine, but many still remain the subject of scientific studies. It is important to note that many inhibitors are peptides, which opens new possibilities for the development of antimicrobial drugs. Another area of peptide application is stimulation of innate immunity, which also could serve as a base for the development of antimicrobial preparations. Phage-derived endolysins that destroy bacterial cell walls and biofilms represent another approach for combating drug resistance. Currently, recombinant endolysins are tested in clinical trials. The development of biocompatible surfaces for transplanted organs is another pressing issue. The review discusses different approaches for creating nanomaterials with antibacterial properties.

The reviews and experimental articles presented in this issue illustrate major directions in the development of methods for overcoming drug resistance and creating novel antibacterial preparations. These studies require deep understanding of genetic and enzymatic processes responsible for the drug resistance. The development of fundamentally new innovative antibacterial preparations is based on recent achievements of modern biological science. Although many approaches presented in this issue are still at the research stage, the obtained experimental results open new horizons for the development effective drugs against infectious diseases.

Ethics declarations. The authors declare no conflict of interest. This article does not contain any studies with human participants or animals performed by any of the authors.

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