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Research Progress on the Mechanisms of Drug Resistance in Common Clinical Microorganisms

Yidan Zheng*
Singapore University of Technology and Design, Singapore 487372, Singapore

**Author to whom correspondence should be addressed.*

Abstract: The popularity of antibacterial drugs has made microbial drug resistance a thorny problem in global public health. In clinical practice, the phenomenon of resistance to antibacterial drugs by common microorganisms, such as bacteria and fungi, is becoming increasingly common. This article focuses on the main molecular mechanisms by which these microorganisms develop drug resistance. It conducts in-depth analyses from multiple aspects such as changes in drug targets, overexpression by drug efflux pumps, horizontal transfer of drug resistance genes, and biofilm formation. Based on the review of the latest progress in drug resistance research, it explores future research directions. It is hoped that it can provide a practical and feasible theoretical basis for clinical anti-infection treatment and prevention and control of drug resistance.

Keywords: Microorganisms; Drug resistance mechanism; Antibacterial drugs; Research progress

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1. Introduction

Microbial drug resistance refers to the phenomenon where microorganisms develop resistance to originally effective antibacterial drugs. In recent years, due to the irrational use of antibacterial drugs, multidrug-resistant strains and "superbugs" have emerged continuously, posing extremely severe challenges to clinical anti-infection treatment [1]. The World Health Organization has listed antibiotic resistance as one of the top ten public health threats worldwide [2]. In-depth research on the mechanism of microbial drug resistance is of great significance for developing new antibacterial drugs and optimizing existing treatment regimens [3–5]. Microorganisms are widely distributed in nature and come in a variety of types, including bacteria, fungi, viruses etc. In the long-term survival competition, microorganisms have been constantly evolving to adapt to environmental changes, and developing resistance to antibacterial drugs is one of their adaptation strategies [6]. Only by understanding the formation mechanism of microbial drug resistance can we formulate more effective prevention and control measures and improve the success rate of clinical anti-infection treatment.

2. The main mechanism of microbial drug resistance

2.1. Changes in the target sites of antibacterial drugs

Microorganisms often cause structural changes in drug targets through pathways such as gene mutations or gene transfer,

thereby reducing the binding ability of drugs to the targets. Take Staphylococcus aureus as an example. It can change the structure of penicillin-binding protein (PBP), thereby developing resistance to β-lactam drugs [7]. Under normal circumstances, β-lactam drugs can specifically bind to PBP, inhibit the synthesis of bacterial cell walls, and thereby exert a bactericidal effect. However, when the PBP structure of Staphylococcus aureus changes, β-lactam drugs cannot effectively bind to it, allowing the bacteria to continue synthesizing the cell wall and thereby developing drug resistance.

2.2. Production of drug-degrading or modified enzymes

Microorganisms can secrete specific enzymes to degrade or modify antibacterial drugs, rendering them inactive. β-lactamase can hydrolyze the β-lactam ring of β lactam antibiotics, which is the main reason why Gram-negative bacteria are resistant to penicillin drugs. The antibacterial activity of β-lactam antibiotics depends on the integrity of the β-lactam ring. After the β-lactamase hydrolyzes the β-lactam ring, the drug loses its antibacterial activity, and Gram-negative bacteria develop resistance to penicillin drugs. Carbapenase can hydrolyze carbapenem drugs. Carbapenem drugs are a kind of broad-spectrum and highly efficient antibacterial drugs, which have good antibacterial activity against a variety of drug-resistant bacteria. However, with the emergence of carbapenase, the resistance of bacteria to carbapenem drugs has gradually increased, bringing great difficulties to clinical treatment.

2.3. Drug efflux pump system

Microorganisms can actively excrete drugs out of cells by overexpressing efflux pump proteins. The AcrAB-TolC system in Gram-negative bacteria can excrete various antibiotics [8]. This system is composed of the inner membrane protein AcrB, the outer membrane protein TolC and the membrane fusion protein AcrA. They work synergistically to pump various antibiotics that enter the bacterial cells out of the cells, reduce the intracellular drug concentration, and cause the bacteria to develop drug resistance.

2.4. Changes in cell membrane permeability

Microorganisms can reduce drug influx by altering the expression or structure of membrane pore proteins. The deletion of the ompK35/36 well protein in Klebsiella pneumoniae can lead to its resistance to carbapenem drugs. The ompK35/36 well protein is an important channel on the outer membrane of Klebsiella pneumoniae. Carbapenem drugs enter the bacterial cells through the well protein to exert antibacterial effects [9]. When ompK35/36 well proteins are missing, carbapenem drugs have difficulty entering cells, and bacteria develop resistance to them.

2.5. Biofilm formation

Microorganisms secrete extracellular polymers to form biofilms with multiple protective effects. Biofilms, as physical barriers, can restrict the penetration of drugs. The extracellular polymers in the biofilm form a complex network structure. When drug molecules pass through the biofilm, they are hindered and have difficulty reaching the surface of bacterial cells, thereby reducing the bactericidal effect of the drugs. The cell metabolism within the biofilm is slow, and the sensitivity to antibacterial drugs decreases [10]. Within the biofilm, the growth rate and metabolic activity of bacteria are relatively low, and they are in a relatively dormant state. Bacteria in this state have a decreased sensitivity to many antibacterial drugs because antibacterial drugs are usually more effective against bacteria that are growing vigorously and metabolically active.

2.6. Horizontal transfer of drug resistance genes

Microorganisms spread drug resistance genes through mobile genetic elements such as plasmids and transposons. Plasmid-mediated drug resistance gene transfer is the main route of drug resistance transmission among Gram-negative bacteria. Plasmids are circular double-stranded DNA molecules that can replicate autonomously and carry multiple drug resistance genes. Gram-negative bacteria can transfer plasmids to other bacteria through conjugation, transformation and other

means, enabling the recipient bacteria to acquire drug resistance.

2.7. Activation of metabolic bypass

Microorganisms can bypass the sites of drug action by altering metabolic pathways. Sulfonamide-resistant bacteria obtain folic acid through exogenous sources. The mechanism of action of sulfonamide drugs is to inhibit the synthesis of folic acid in bacteria. However, sulfonamide-resistant bacteria can take up ready-made folic acid from the environment, thereby bypaching the effect of sulfonamide drugs and developing resistance to them. Some bacteria can activate alternative enzyme systems to maintain basic life activities when antibacterial drugs inhibit their normal enzyme systems [11]. In this case, the bacteria continue their metabolic activities to survive, thereby demonstrating resistance to the antibacterial drug. This metabolic bypass activation mechanism enables bacteria to adapt to the environment by adjusting metabolic pathways when facing the stress of antibacterial drugs, thereby enhancing their survival ability.

3. Research progress on special drug resistance mechanisms

3.1. Post-translational modification of proteins and drug resistance

In recent years, the key role of post-translational modifications of proteins in the formation of drug resistance has gradually attracted academic attention. Take *Escherichia coli* as an example. YjgM crotonyltransferase can modify the transcription factor PmrA, thereby up-regulating the lipopolysaccharide modification gene, causing the bacteria to develop resistance to polymyxin. Under normal conditions, the expression regulation of lipopolysaccharide modification genes by PmrA is maintained at a specific level. However, when YjgM crotonyltransferase acts on PmrA, the activity of PmrA changes and can bind more tightly to the promoter regions of the phosphoethylamine transferase EptA and the glycosyltransferase PmrK/ArnT genes, promoting the expression of these genes. This series of changes eventually led to an increase in the lipid A modification level of the bacterial outer membrane lipopolysaccharide (LPS), a change in the outer membrane structure, making it difficult for polymyxin to bind to it, thereby generating resistance.

3.2. The regulatory effect of synonymous mutations on drug resistance

For a long time, the traditional view holds that synonymous mutations do not affect protein functions. However, the latest research has found [12] that synonymous mutations of the hisD gene (522 G > A and 972 C > T) can regulate bacterial resistance to fluoroquinolone drugs by affecting the translation rate and protein conformation. Under normal circumstances, the expression products of the hisD gene play an important role in the bacterial metabolic process and are closely related to the resistance of fluoroquinolone antibiotics [13–15]. When the hisD gene undergoes the above synonymous mutations, although the amino acid sequence of the encoded protein remains unchanged, the secondary structure of the mRNA may change, affecting the movement speed of the ribosome on the mRNA, that is, the translation rate. The change in translation rate further affects the folding process of proteins, resulting in conformational changes of HisD proteins. After this conformational change, the HisD protein loses its normal regulatory function for downstream genes, such as being unable to up-regulate the expression of sbmC and umuD genes, thereby affecting the mutation frequency of the gyrA gene and ultimately altering the bacteria's resistance to fluoroquinolone antibiotics.

3.3. Interaction between bacteriophages and bacterial drug resistance

There is a potential association between the defense mechanism of bacteria against bacteriophages and antibiotic resistance. Bacteria mainly resist phage infection through the CRISPR-Cas system, restriction modification system, etc. Among them, the CRISPR-Cas system, as an important component of bacterial adaptive immunity, is capable of recognizing and cutting the DNA of invading bacteriophages to protect bacteria from infection. The restriction modification system resists phage invasion by methylating its own DNA and simultaneously recognizing and cutting unmethylated exogenous DNA, including phage DNA. On the other hand, bacteriophages have also evolved corresponding strategies in order to

successfully infect bacteria. Some bacteriophages can encode specific antagonistic proteins, which can act on the defense proteins of bacteria. For instance, by phosphorylation modification, the activity of bacterial defense proteins can be altered, interfering with the defense mechanisms of bacteria, thereby enabling bacteriophages to successfully infect bacteria [16]. During this process, the physiological state of bacteria may change, thereby affecting their sensitivity to antibiotics.

4. Prospects of new anti-drug resistance strategies

Researchers are actively exploring effective strategies to deal with the drug resistance situation. Given its increasingly severe current situation, these explorations are extremely urgent. In the field of new antibiotic research and development, the lasso peptide antibiotic lariocidin has demonstrated unique advantages. It acts on brand-new sites on the ribosome that have not yet been reached by traditional antibiotics, making it difficult for bacteria to rapidly develop resistance to them through common genetic mutation methods. By interfering with the synthesis process of bacterial proteins, lariocidin has opened up a new path for the clinical treatment of drug-resistant bacterial infections, effectively compensating for the frequent occurrence of bacterial resistance caused by the extensive use of traditional antibiotics.

Phage therapy is to treat infections by taking advantage of the specific infection characteristics of phages against drug-resistant bacteria. Because bacteriophages have a high degree of host specificity, they can precisely identify and invade specific types of bacteria. During the treatment process, bacteriophages can directly attack drug-resistant bacteria and achieve the therapeutic goal by lysing bacterial cells. Research has found [17] that some antagonistic proteins encoded by bacteriophages can interfere with the defense mechanism of bacteria and enhance the infection ability of bacteriophages. The combined use of these antagonistic proteins with bacteriophages or the expression of antagonistic proteins in bacteriophages through genetic engineering modification is expected to further enhance the therapeutic effect [18].

The combination medication strategy is a multi-target treatment plan designed for the complex and diverse drug resistance mechanisms of microorganisms. A single drug is often difficult to deal with complex drug resistance situations. However, the combined use of antibacterial drugs that act on different targets can simultaneously target multiple drug resistance mechanisms of bacteria and reduce the possibility of bacteria developing drug resistance. For instance, the combined use of drugs that inhibit the synthesis of bacterial cell walls and those that inhibit protein synthesis can attack bacteria from multiple perspectives, significantly enhancing the bactericidal effect.

5. Conclusion

The mechanism of microbial drug resistance is extremely complex and diverse in form. Different mechanisms often collaborate and act together, thereby triggering a high level of drug resistance. In recent years, with continuous breakthroughs in disciplines such as omics technology, structural biology, and synthetic biology, our understanding of drug resistance mechanisms has also been continuously deepened. In future research, the deep integration of basic research and clinical application is extremely urgent. Basic research should continuously explore the brand-new mechanisms of microbial resistance to lay a solid theoretical foundation for the development of new anti-infective drugs and strategies. Clinical application requires the timely transformation of basic research results into practical and feasible treatment plans, and the verification and optimization of new therapies through clinical practice. Meanwhile, regulating the use of antibacterial drugs is of great significance. Relevant departments should strengthen the supervision of the use of antibacterial drugs, enhance the awareness of clinical doctors and the public to use antibacterial drugs rationally, reduce unnecessary medication behaviors, and prevent the emergence and spread of drug resistance from the root. Only by taking multiple measures and jointly addressing the challenge of drug resistance can the continuous research on the mechanism of microbial drug resistance lay a solid foundation for clinical anti-infective treatment, which is of immeasurable value for ensuring public health security.

Disclosure statement

The author declares no conflict of interest.

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