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Research on novel antibiotics: Bacterial division inhibitors

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Abstract. We all know that bacterial infections can cause many diseases, which can affect the normal life of people and even seriously threaten life safety. But now, many antibiotics in use have developed resistance, and the form of antibiotic resistance is becoming more and more serious. Although several treatment methods have been found that can not rely on antibiotics, there are certain shortcomings in terms of cost and treatment effect. So, the hardest but most effective way is to develop new antibiotics. Bacterial division is an important process of bacterial growth and reproduction, and its inhibitors have great potential to become new antibiotics. Therefore, this paper introduces the inhibitors of bacterial division.

Keywords: Antibiotics, Antibiotic resistance, Bacterial division, Inhibitors.

1. Introduction

Alexander Fleming, an Englishman, first discovered penicillin in 1929, and to this day, penicillin and other subsequently discovered antibiotics have been widely used, saving many lives. Bacterial infections are usually treated by antibiotics, which have extended the average human lifespan by many years. Antibiotics are substances produced by bacteria, fungi, actinomyces, or higher plants and animals that can inhibit or even destroy other microorganisms at a very low concentration. Antibiotics can be extracted directly during the growth and reproduction of some microorganisms, or they can be synthesized artificially. Antibiotics not only can inhibit or kill bacteria but also can inhibit viruses, fungi, and even tumors.

2. Harm of antibiotic resistance

With the continuous research on antibiotics, different kinds appear one after another. However, there is no good command of the dosage of antibiotics. On the one hand, researchers still have some difficulties with the rational dosage of antibiotics. On the other hand, some patients are too dependent on antibiotics and don't take antibiotics in the correct amount, which leads to abuse of antibiotics. which has a lot of harm: First, will induce antibiotic resistance, and there are more and more resistant bacteria; second, when bacteria inside and outside of the human body develop antibiotic resistance, it will damage human organs and endanger life safety; third, it will lead to double infection, Under normal circumstances, there are many bacterial parasites in the human body, and various bacteria maintain a balanced shape. After long-term use of antibiotics, sensitive strains in the human body will be killed, while insensitive strains or various fungi and other strains that have not been inhibited will parasitize the human body at this time, resulting in secondary infection. And the double infection can often endanger the life of patients; last, it

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will be harmful to society. The misuse of antibiotics can lead to resistance in certain bacteria in a given area, making treatment more difficult.

However, due to the overuse of antibiotics, antibiotic resistance has developed and gradually increased. Antibiotic resistance means that bacteria are not sensitive to antibiotics, and once antibiotic resistance is produced, the treatment effect of antibiotics will be obviously weakened. There are already a number of bacterial infections that show resistance to antibiotics.

The resistance of drug-resistant bacteria has become a global problem, and it has been reported the Multidrug-resistant, extensively drug-resistant, and pan-drug-resistant strains of Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa in the world [1].

3. Current situation and development of antibiotic application in China

China is one of the most serious countries in the world where antibiotics are abused. The resistance of some bacteria isolated during treatment is already among the highest in the world, and some experts believe that China may be the first country to enter the "post-antibiotic era," which will be a disaster. In the 1990s, there were penicillin-resistant Streptococcus pneumoniae, fungi, and methicillin-resistant Staphylococcus aureus enterococcus . In addition, there are also pseudomonas aeruginosa, which is highly resistant to amoxicillin, zinacef, and other antibiotics, and Klebsiella pneumoniae, which is highly resistant to a variety of antibiotics, such as Ciliacin and fusidacin. The infection of drug-resistant bacteria makes a more serious threat to humans. At present, many bacterial infections are infections of drug-resistant bacteria, and the treatment effect of antibiotics is poor or has no effect, so most drug-resistant bacterial infections will eventually lead to death. Antibiotic resistance means that the therapeutic effect of antibiotics is not as good as before. Still, the development of new antibiotics is very slow, and the development rate of antibiotics is far less than the emergence of drug-resistant bacteria. This means that we need to think about what we are going to do if one day there is a bacteria that is resistant to all antibiotics, and if that happens, it is going to be devastating for humanity. So now we must accelerate the research and development of new antibiotics, looking for everything that could develop new antibiotics.

The overuse of antibiotics has led to a gradual increase in antibiotic resistance. However, the slow development of new antibiotics has led to longer but less effective treatments and increased mortality due to bacterial infections. Therefore, antibiotic resistance has become a major threat to medical health, and the prevention and treatment of drug-resistant bacteria have become more serious [2]. Methods such as microbiome therapy, phagocytosis, or antitoxic therapy are available. Still, these methods can not solve the problem fundamentally, so the most effective way is to develop new antibiotics [3]. Bacterial division inhibitors are promising as new antibiotics. Most antibiotics currently in use target the synthesis of DNA, RNA, protein, or cell wall. But now, there are pathogens with reduced sensitivity to antibiotic treatment, so we must find new antibiotics with new targets and mechanisms of action [4]. Most bacteria divide in two ways and differentiate very quickly [5]. The result of bacterial division is the production of two daughter cells of similar size, which were derived from a mother cell [6]. The cell division of most bacteria is driven by the FtsZ protein to form a hydrodynamicZ ring [7,8]. It can be seen that bacterial division is an important part of the process of bacterial growth and reproduction, and bacterial division inhibitors can inhibit bacterial growth by inhibiting bacterial division, so when bacterial infection occurs, it is expected to be treated by bacterial division inhibitors, but whether it can be used in humans needs to be proved by subsequent specific experiments. But we need to first have a certain understanding of bacterial division inhibitors, from which we can screen substances with the potential of new antibiotics.

4. The concept and classification of Bacterial division

Bacteria belong to the prokaryote kingdom, with a simple cell structure and no mitochondria, chloroplasts, or nuclei. They are single-celled microorganisms with tiny individuals. Most can only be observed under a microscope, a wide variety of creatures, the largest of all the variety of shapes, mainly spherical, rod, and spiral. Bacteria have a great influence on human activities, with advantages, such as

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the making of cheese, yogurt, and wine, and some antibiotics, but also harmful ones, such as bacterial infections.

Bacteria can be classified into cocci, bacilli, and spirulae according to their morphology, Gram-positive bacteria and Gram- negative bacteria according to their cell wall components. Aerobic bacteria and anaerobic bacteria can be divided according to whether oxygen is needed, and autotrophic bacteria and heterotrophic bacteria can be divided according to lifestyle. Bacterial classification is now based on phenotypic analysis based on numerical taxonomy, chemical taxonomy and genotypic classification [9].

Bacterial infections can cause many diseases: Staphylococcus saprophyticus, Proteus mirabilis, Klebsiella pneumoniae, Enterococcus faecalis, and Escherichia coli, can lead to urinary tract infections streptococcus[10], Can lead to post-infectious glomerulonephritis Helicobacter pylori, Chlamydia psittaci, Coxeria bainei, Borrelia burgdorferi, and Campylobacter jejuni,associat with non-Hodgkin's lymphoma [11,12]. Here are just four examples, but there are many other diseases associated with bacterial infections.

The bacterial division procedures: the first step is that the nuclear of the cell should be replicated, and the cell will elongate; the second step is that the cell will form a diaphragm; the third step is that the cell will form a new distinct cell wall; the last step is a cell was divided, and the two daughter cells will separate. Bacilli usually divide along the transverse axis. FtsZ first needs to bind GTP, and then multiple FtsZ monomers self-polymerize to form the precursor fiber, forming the main framework of the contraction ring. At the later stage of bacterial division, the constriction ring is contracted to complete bacterial division. The cell division of bacteria is a very important process with great potential for development[13]. Here are several bacterial cell division inhibitors from literature.

5. Major Bacterial Division Inhibitors

PC190723 Effect on FtsZ: Influence on FtsZ GTPase activity, Stabilize FtsZ polymers, Mislocalize FtsZ [4]. It is a benzamide derivative with a thiazolopyridine fragment and is a synthetic compound. It has potent in vitro bactericidal activity against Staphylococcus including multidrug-resistant Staphylococcus aureus. Curcumin Effect on FtsZ: Influence on FtsZ GTPase activity, Disturb FtsZ assembly[14]. Curcumin is a polyphenol compound with a diketone structure. It contains a special 1,7-diarylheptane skeleton consisting of one β diketone and two ortho-methylated phenols. It also inhibits cyclooxygenase-2, lipoxygenase, and inducible nitric oxide synthase and other inflammation-related enzymes are expressed in the body, thereby reducing the inflammatory response. Chrysophaentin A Effect on FtsZ: Influence on FtsZ GTPase activity, Disturb FtsZ assembly [4]. It has antibacterial action and wide antibacterial spectrum, and it can also hinder the synthesis of nucleic acid and protein in bacterial cells, inhibit the abnormal metabolism of eicosenoic acid, and has a significant inhibitory effect on common fragile bacilli. In addition, it scavenges free radicals. Zantrin Z3 Effect on FtsZ: Influence on FtsZ GTPase activity, Stabilize FtsZ polymers [4]. It has antibacterial effect and can inhibit the synthesis of bacterial cell wall. Respiratory tract infections, skin soft tissue infections, urinary tract infections, abdominal cavity infection and other infectious diseases could be treated by it.

Berberine Effect on FtsZ: Influence on FtsZ GTPase activity, Disturb FtsZ assembly, Mislocalize FtsZ; It can also inhibit bacterial DNA replication and transcription, inhibit protein synthesis, and inhibit the activity of important enzymes in bacteria. Its antibacterial mechanism is similar to rifampicin and norfloxacin. He has a strong inhibitory effect on the long secretion disorder caused by E. coli thermostable enterotoxin and Vibrio cholerae toxin. In addition, he also has the function of regulating blood sugar, anti-tumor function, anti-atherosclerosis function, reducing blood uric acid function, anti-rheumatoid arthritis function, anti-heart failure, and improving cardiopulmonary function, inhibiting of platelet aggregation, blood lipid-lowering, blood pressure lowering, antiarrhythmic effect, the effect of inhibiting cardiac hypertrophy, the effect of treating hyperthyroidism, the effect of treating urinary tract infection during pregnancy, anticancer effect. Coumarins Effect on FtsZ: Influence on FtsZ GTPase and polymerization activity [15]. It is a class of aromatic oxygen-containing heterocyclic compounds and can inhibit DNA helicase. It was found in Solanaceae, Rutaceae and Umbelliferae. It is antibacterial, antiviral and anticoagulant. It can be used to treat diseases such as pneumonia and septicaemia.

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Coumarins with long-chain substituents have a better antibacterial effect. Ciinnamaldehyde Effect on FtsZ: Influnce FtsZ function [16].

Cinnamaldehyde is a yellow transparent oily liquid with cinnamon and burnt aroma. It is easily soluble in alcohol and ether, volatile with water vapor, easy to be oxidized in air, and unstable in strong acid or alkali environments. It can increase the permeability of bacterial cell membrane and cell wall, inhibit protein metabolism and biofilm formation, and reduce quorum sensing effect. Cinnamaldehyde has antioxidant groups such as hydroxyl group and double bond, which can protect intestinal mucosa and reduce diseases caused by oxidative stress. In addition, there are some substances that have inhibitory effects. Effect on FtsZ: Influence on FtsZ GTPase activity, Stabilize FtsZ polymers, Mislocalize FtsZ; Effect on FtsZ: Influence on FtsZ GTPase activity, Disturb FtsZ assembly; Effect on FtsZ: Influence on FtsZ GTPase activity, Stabilize FtsZ polymers; CCR-11 Effect on FtsZ: Influence on FtsZ GTPase activity, Disturb FtsZ assembly, ADEP1 Effect on FtsZ: Affects degradation of FtsZ, ADEP4 Effect on FtsZ: Affects degradation of FtsZ, [4] Benzodioxane-benzamides Effect on FtsZ: Interfering with FtsZ function[17]; UCM05 and its simplified analogue UCM44 Effect on FtsZ: Influence on normal assembly and specific binding of bacillus subtilis FtsZ monomer[18]; 2,6-difluorobenzamide Effect on FtsZ: Influence on the FtsZGTPase [19]. It is a white powder crystal that needs to be protected from light and can be used to make pesticides. Novel 3-elongated arylalkoxybenzamide derivatives Effect on FtsZ: Influence on FtsGTPase [20]. It has antibacterial action against Bacillus subtilis and Staphylococcus aureus. It can also be used to make pest control agents. Isoquine Effect on FtsZ: Influence on FtsZ polymerization and/or GTPase activity. It is colorless flake crystals, solid or liquid, and has a fragrance. It is found in coal tar. Slightly soluble in water and a variety of organic solvents. It can be used to synthesize drugs, dyes, insecticides and gas chromatography fixatives. Guanine nucleotide Effect on FtsZ: Interfere with FtsZ polymerization and/or GTPase activity Carbonyl pyridine Effect on FtsZ: Interfere with FtsZ polymerization and/or GTPase activity 4-and 5-substituted 1-phenylnaphthalene Effect on FtsZ: Interfere with FtsZ polymerization and/or GTPase activity [21].

6. Conclusion

These substances can inhibit bacterial growth by inhibiting bacterial division, and they all inhibit bacterial growth through the action of the key protein FtsZ that affects cell division. Since bacterial division is an important step in bacterial growth and reproduction, its inhibitors have great potential as new antibiotics. Now that the global situation of antibiotic resistance has become more and more serious, we must accelerate the development of new antibiotics. Bacterial division inhibitors provide us with a new direction. Bacterial division key protein FtsZ also provides us with a new antibiotic target.

These cell division inhibitors all act by affecting the function of FtsZ, a key protein of cell division, and some of them affect the dynamic assembly of FtsZ protein. Some of them affect GTPase activity of FtsZ protein. We can find that FtsZ is not only a key protein in bacterial division but also has a great potential target being new antibiotics [22-24]. The cell division of bacteria is accomplished by FtsZ protein-ntered complex, which is polymerized into a Z loop that directs peptidoglycan synthesis to drive contraction [25], FtsZ is a eukaryotic tubulin homologue, a GTP-development prokaryotic cytoskeleton protein. FtsZ self-assembles into dynamic filaments and forms dynamic Z-loops in the center of bacterial cell, leading to separation and subsequent the cell division of bacteria [23]. In recent years, it has been found that bacterial division is initiated and completed by the Z-loop formed by FtsZ protein. Z - ring is the key structure for bacteria to complete division. It usually comprises the key protein FtsZ and dozens of different proteins. Inhibition of Z - ring will lead to slow growth and death of bacteria. Therefore, FtsZ, the key protein of Z-ring, and other related proteins are ideal targets for developing new antibiotics.

Most of the antibiotics used in the clinic have become resistant to antibiotics. Many bacteria have become resistant to antibiotics, and treatment after infection by such bacteria becomes complicated and more difficult. So we need new antibiotics that can inhibit multidrug-resistant bacteria. In the current research, FtsZ is considered to be the most promising target and the approach targeting FtsZ is considered to be the most likely therapeutic approach. Some new antibiotics have been shown to

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influence on the natural dynamics and function of FtsZ during bacterial cell division or to activate bacterial proteases to cause bacterial death. Such drugs can work in infected animal models, but more experiments are needed to verify whether they can be used in clinical medical procedures.

Although inhibitors of bacterial division have the prospect of becoming new antibiotics, we should not be blindly optimistic. On the one hand, there are many potential bacterial division inhibitors or other substances that may become new antibiotics that we have not yet discovered; on the other hand, whether known bacterial inhibitors can be used in the human body needs a lot of research, and whether they can be used in the clinic is still a huge challenge. Progress in developing new antibiotics is slow, but the trouble of antibiotic resistance is urgent. We should pay attention to antibiotic resistance, and we should not continue to abuse antibiotics so as not to lead to more serious antibiotic resistance.

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