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Therapeutic strategies against antibiotic resistance

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Abstract. Antibiotics are the most important class of drugs and are one of the most influential medical inventions of the 20th century. Antibiotics have undoubtedly been a benefit to human society in the fight against bacteria, saving millions of lives. However, the number of infections caused by multidrug-resistant bacteria (MDR) is rising. Although antibiotics have enabled the development of several of medical practice, including the effective outcomes of several surgical and immunosuppressive therapies that rely on antibiotic prophylaxis and the potential to manage infectious complications, antimicrobial resistance poses significant challenge for all healthcare systems worldwide. As all organisms develop genetic mutations to prevent lethal selection, antimicrobial resistance is an inevitable evolutionary outcome. Bacteria will tend to develop and use resistance strategies as long as antibiotics are used against them. This review was based on the latest international information about therapeutic strategies against antibiotic resistance (by electronic search using Pubmed, SciFinder, Scirus, GoogleScholar and Web of Science).

Keywords. resistance, antibiotics, mechanisms, strategies, perspectives

1. Introduction

Microscopic organisms, such as bacteria, are living things that adapt in time. Their main purpose is to multiply, survive and spread as far as possible and quickly as possible. Microbes therefore adapt to their environment and evolve in ways that ensure their continued existence. If something hinders their ability to grow, such as an antibiotic, genetic changes can occur and make the bacteria immune to the drug and allow it to survive. It is a natural process for bacteria to develop drug resistance. However, there are currently several factors that contribute to the complex aetiology of antibiotic resistance. These include the use of overuse and abuse of antibiotics, inaccurate diagnosis and inappropriate prescribing of antibiotics, loss of patient susceptibility and self-medication, health conditions, inadequate sanitation, poor personal hygiene and widespread use in agriculture [1]. With the rapid and global emergence of multidrug-resistant bacteria, there is a need to new antibiotic therapy techniques. Antibiotics are now in development and others even in preclinical testing. The potential for expansion is provided by biological substances and non-antibiotic adjuvants. The administration of antimicrobials, new antibiotic molecules, biological substances and mechanisms of distribution must all be integrated into successful combination treatments that: combat infection, prevent resistance and ensure maintenance of the normal microbiome. There are several approaches that need to be adapted to combat antimicrobial resistance [2]:

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2. Multi-pathway approaches in combination

A variety of successful combinations acting through different pathways use non-antibiotic adjuvants. Because of the diversity of pathways, combining antibiotics with adjuvants is a leading approach in combating the process of resistance to multiple medically. Rifampicin, minocycline and chlorhexidine are just a few examples of such of combinations. Antiseptic inhibitors and other natural compounds (e.g.plant derivatives) or biologicals (e.g. bacteriophages) are three typical adjuvants that have been successful therapeutic. Tranquilisers, antihistamines, antispasmodics, antihypertensives and anti-inflammatory drugs are among the groups of substances known to be investigated as adjuvants to antibiotics [2].

3. Strategies that work in similar ways in combination

The hybrid technique can target various biomolecules acting in the same pathway. Even if it is a less diversified approach than attacking various pathways, it can be a strategy very effective if the right path is selected. The routing option is limited by two factors. First, the targeted pathway must be an absolute necessity for survival, such as the need for folate for the synthesis of deoxythymidine monophosphate (dTMP), a precursor of deoxyribonucleic acid (DNA) synthesis. Second, the pathway cannot be necessary, as this makes the technique vulnerable to opposition. In the face of increasing antibiotic resistance, focusing on different steps in the same pathway is an approach risky, but it is also more effective than monotherapies in certain situations [2].

4. Approaches acting on the same targets in combination

Targeting two separate biomolecules within the same pathway is less variable than heading down two completely different paths, but it is more diverse than use of two monotherapies to suppress similar biomolecules. A classic example of antibiotics that target bacterial ribosomes is Synercid (quinupristin/dalfopristin), a hybrid of two semi-synthetic drugs in which the components bind to the region neighbouring 50S ribosomal subunits, demonstrating the efficacy of this strategy as is far more effective than any drug used alone. Due to the structure essential and conserved bacterial ribosome, the combination of drugs that act on it can be useful [3].

5. Polymicrobial infections in complex approaches

Combination therapies are crucial for treating polymicrobial infections (e.g. abdominal infections, in which both strict anaerobes and bacteria are found intestinal), along with combinations that are effective against a single agent periprosthetic joint infection is caused by the involvement of several pathogens in 4-27% of cases; therefore, the ability to simultaneously and rapidly treat multiple pathogens becomes a critical weapon in the fight against infection. It is important to mention that hybrid treatments should not be limited to just two combinations of drugs. In compared to the two antibiotic combinations, the three antibiotic combinations have proven to be even more effective against extremely resistant strains of *Staphylococcus aureus multicilinus* drug-resistant. In addition, combinations of antibiotics have different modes of action [3].

6. Drug formulations with synergistic effects and resistance

Despite multiple selective pressures, a combination of drugs could encourage the development of drug resistance, despite the initial appearance that the use of a drug combinations will help to avoid several resistance mechanisms.

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This could be because in vitro tolerance to some antibiotics improves susceptibility to other antimicrobials, as shown by increasing minimum concentrations inhibitors. Due to the evolution of multidrug-resistant bacteria (MDR) variants, Drug cocktails will also increase the risk of extreme infections.

To combat this challenge, creating effective drug formulations is a critical step in reducing the proliferation of antibiotic-resistant microbes, while improves the efficacy of drugs and extends the utility of individual agents [4].

7. Molecular enforcement and antibiotic resistance

Antibiotic-resistant bacterial strains have emerged rapidly, making the fight more difficult against infectious diseases and the production of new antibiotics. As an adaptive immune system bacterial, the system frequently clustered between short repeated palindromic intervals - associated with CRISPR (CRISPR-Cas), known as one of the latest methods to combat antibiotic-resistant strains.

The CRISPR-Cas system has been identified as a form of adaptive immune system to bacteria. They have been used for genome editing and a variety of other applications, including the treatment of hereditary diseases [5]. CRISPR systems operate in a similar to RNA interference in eukaryotic cells. Approximately half of bacterial genome and 87% of the archaeal genome contain the framework. Cas proteins are important functional elements that are encoded upstream of the CRISPR array and controls how the mechanism works [6]. In several studies, the CRISPR mechanism has been shown to have a negative relationship significant with resistance to some bacteria, such as enterococci. CRISPR1-Cas, CRISPR2 orphan, absence of Cas and CRISPR3-Cas mutations are the three CRISPR loci detected in *E. faecalis.* Pheromone-responsive plasmids are considered essential in the plasticity enterococcal genome and virulence [7]. Strains of *Streptococcus thermophiles* containing the CRISPR gene have acquired new spacer that comes from the virus, which gives them immunity to phage infection. In *Escherichia coli*, 4 CRISPR loci are present: CRISPR1, CRISPR2, CRISPR3 and CRISPR4. CRISPR does not influence plasmids in *Escherichia coli* or the distribution of genes that encodes antibiotic resistance. These observations contradict those of Palmer and Gilmore, who found that CRISPRs are inversely proportional to tolerance to antibiotics in enterococci [8].

The amount of repetition is a strong measure of the potential effectiveness and honesty of system. Cas proteins are guided to directly target and cleave DNA through ribonucleic acid (RNA)-based spacers surrounded by partial repeats. Recent research has shown that targeting bacterial genome sequences using the CRISPRCas system, intentionally or accidentally, is cytotoxic and can lead to cell death.

For formation of ribonucleic acid (RNA)-guided nuclei, it will be necessary to extract and produce a carrier and distribution vector. Furthermore, thanks to the delivery mechanism used at higher species, ribonucleic acid (RNA)-guided nuclei may be able to modulate the presence of specific genes in the wild-type population, i.e. tolerance genes to antibiotics and virulence determinants [8]. To treat the therapeutic strain of *S.aureus* USA300, cas9 and crRNA of the mecA90 methicillin resistance gene in phagmid (pDB121: mecA) have been prepared. Cell death was not reported in any of the Cas9 plasmids targeting tetracycline-resistant plasmids. After delivery of the CRISPR-Cas, bacteria can be re-sensitized to antibacterials or destroyed, depending on the antibacterial resistance gene target or critical gene target. Distribution based on conjugation, beech-based delivery and polymer nanoparticle-based delivery are among possible delivery routes. Treatment with Cas9-bPEI complex could dramatically reduce 32%

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increase compared to treatment with Castex complex without sgRNA. This discovery could pave the way for the development of antimicrobial drugs based on CRISPR.

The CRISPR-Cas method can also be used to modify the structure of various groups of bacteria. Existing treatments that use drugs to change human microbiota have the ability to relieve pain caused by a variety of diseases, but Citorik and his collaborators argue that the processes by which they operate are still insufficiently understood. An in vivo mouse model was used to evaluate the efficacy of Cas9 phagemid against bacteria. In situations where bacterial species are particularly immune to current antimicrobial agents, phagemid may be a suitable replacement.

For planktonic and biofilm environments, most reports propose a mixture of systems delivery based on phage, conjugative and polymeric nanoparticles. Also, the extinction of intentional organisms and the absence of special methods of monitoring the pathogenic organisms are major problems in modulating the microbiome, microbiology and infectious disease control. CRISPR-Cas-based antibacterials may encounter challenges from CRISPR-Cas vectors or distribution carriers, as well as from complex bacterial communities [9].

8. Bioinformatics in combating antibiotic resistance

Bioinformatics revolutionises and fascinates the field of science and technology. In currently, homology modelling is used to create 3D models to test or validate desired results. Bioinformatics has revolutionised molecular biology research by understanding the structures of macromolecules. Bioinformatics has provided basic tools to develop ideal drug strategies to address the growing problem of antibiotic-resistant microbes. Bioinformatics deals with the study and understanding of different data forms of macromolecules and their interactions [10].

9. Whole genome sequencing (WGS)

Whole genome sequencing of a pathogen has recently become a method vital for genotyping. Use for whole genome analysis could provide information on the associated bacterial lineage and could revolutionize hospital outbreak research. Genome sequencing provides a framework solid for scientific progress, especially in biomolecular modelling and design drugs, with a focus on antibiotic resistance. Technology platforms and high throughput bioinformatics can provide new insights into virulence, disease spread and antimicrobial tolerance, in addition to faster and more accurate detection of pathogens than conventional approaches. DNA sequencing is an excellent tool for protein modelling and drug development. In addition, significant advances in protein expression, gene sequencing, nuclear magnetic resonance and crystallography have changed the possibilities of using the three-dimensional architecture of the proteins to accelerate drug discovery. This is one of the most important techniques for combating bacterial resistance, as it allows detection of possible family members, aligning sequences and modelling three-dimensional structures [11].

10. In silico serovar, serogroup and antigenic profile study

As classical serotyping has been replaced by molecular serotyping, the development technologies, whole genome sequencing (WGS) has become very important in genotyping. Genes encoding the surface antigen, constituting the core genome, type (MLST) and serovar-specific markers are used in current approaches to in silico prediction of serovar. However, only a few serovars can be distinguished using serovar-specific markers. Zhang and his collaborators developed a method computational serovar prediction by comparing 1089 genomes indicating 106 serovars with a range of 131 serovar-specific markers. According to the researchers, this technique has been a valuable screening tool for genomic studies. It can

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be used not only to classify a particular class of genetic markers, but also to create inexpensive tests to detect specific genetic markers of major serovars [12].

11. Metagenomics for antimicrobial surveillance

Metagenomics strategies depend on next-generation sequencing data with short read (SR-NGS), which allows quantification of thousands of transmissible resistance genes in a single sample without the use of predefined genes. Thus, it can provide more information about the existence of bacterial organisms, pathogens and virulence genes, and the data obtained can be re-analysed if new genes of interest are discovered.

Metagenomics has recently been shown to be more effective than traditional surveillance of antimicrobial resistance in pig herds, and has been used with successfully to compare antimicrobial resistance in animals, as well as in investigations epidemiological evidence. Because of its advantages, metagenomics has a future promising as a method for surveillance of antimicrobial resistance. This could lead to a point surveillance of antimicrobial resistance, allowing the identification of all resistance genes [13].

12. Comprehensive Antimicrobial Resistance Database (CARD)

CARD is a meticulously assembled platform that provides detection patterns, sequences of macromolecules and computational resources for understanding the molecular mechanism of antimicrobial resistance. CARD is a database that focuses on providing high-quality reference data and molecular sequences in a vocabulary specific. CARD's Resistance Gene Identifier (RGI) program is used in the Ontology Antibiotic Resistance (OAR), which was created by the CARD biocuration team to integrate with software development activities for resistance analysis and prediction.

CARD usage increased in 2017 as a result of widespread cleaning of the sequences of reference, modification of the ontological framework, introduction of a new classification methodology and the expansion of bioanalytical methods. The most recent module on resistance and variants, e.g. includes interpretation and statistical summary of expected strength variants from 82 microorganisms and over 100,000 genomes. Expected resistance can be summarized using CARD data, and the antimicrobial resistance mobility models can be identified by including these resistance variants in CARD [14].

13. Bacteriophages - a therapeutic strategy

The development of bacteria resistant to antimicrobial drugs is now the biggest challenge in the treatment of bacterial infections, so attention is paid other possible alternative targets. Many advantages of using the treatment have been mentioned with beech versus chemotherapy, and seems to be a potential drug to replace antibiotics, based on the good findings of phage therapy. Bacteriophages can be distinguished from other antibacterial agents in several ways, including the production of virolysin, encoding antimicrobial peptides, the delivery mechanism for genes encoding antimicrobial compounds and the ability to infect susceptible bacteria as a live phage [15]. Beech can also be used to deliver drugs**.** Beech transfer genes encoding antimicrobials or harmful antimicrobials into target bacteria during this process. In addition, filamentous beeches can deliver therapeutic genes to mammalian cells. During this process, mammalian cells are transduced through receptor-mediated endocytosis. This method is not antibacterial per se, but can be further developed to deliver antibiotic genes to intracellular bacterial pathogens. Treatment with bacteriophages, which was mainly used almost a century ago, is experiencing a renaissance, largely due to the problem of antimicrobial resistance. Strictly beech lysogens, proven antibacterial efficacy

against the target pathogen and elimination of contaminated bacterial debris and endotoxins are recommended regulated conditions for the therapeutic use of beech [15]. In addition, the receptor of the bacterial host for any therapeutic phage, as this will provide information on the emergence of beech resistance, evolutionary trade-offs and adoption of associated treatments that are less likely to create beech-resistant hosts.

Binding to specific receptors on the bacterial host surface is the first step in infection lysogenic with beech. These receptors can be found on the cell wall of gram-positive bacteria or gram-negative, polysaccharide capsules and even appendages such as pili and flagella. the range of hosts that a phage can infect is generally determined by the blocking interaction and key between phage and bacterial receptors, and the list of described phage receptors is continuously development. After adsorption, the virus will inject its genetic material into the host [16].

14. The bird egg model as a therapeutic strategy against antimicrobial resistance

Bird immunoglobulin is a "supermedication" that should be evaluated immediately in the fight against antibiotic resistance worldwide. Antibodies from in birds meet all the above criteria and have the potential to be an alternative effective against antibiotics and other antimicrobials in the fight against antimicrobial resistance. The immune system has always been the strongest defender against disease in people, animals and birds. By using egg as a source, polyclonal antibodies have been produced specific for a wide range of infectious, including viruses, bacteria and parasites, that do not affect the normal flora. The virus then invades the replication machinery bacterial growth, leading to the production of new generations of beech trees. Replication will continue until phage-encoded proteins are activated to lyse the cell and kill the host, allowing newly manufactured viruses to escape and start the cycle again. The lysis period, called and the latent period, is the time required for a beech to complete an intracellular life cycle [17].

15. Cytokines in antimicrobial resistance therapy

Antibodies play an important role in maintaining body homeostasis and functioning appropriate immune system. T cells, which produce numerous interleukins (IL), which activate antimicrobial processes in mononuclear phagocytes, are largely responsible for acquired resistance to intracellular microorganisms. Role of interleukins in antimicrobial infections was clarified by experimentally infecting mice with *Mycobacterium bovis* and *Listeria monocytogenes.* One study showed that IFN- decreases the amount of *L. monocytogenes*, and anti-IFN- antibody therapy makes the situation worse; more than both, IFN, IL-4 and IL-6 activate macrophage processes with tuberculostatic properties and listericidal in vitro. Anti-TNF antibodies aggravate listeriosis and interfere with development granuloma induced by *M. bovis*; simultaneous application of mycobacterial products and Tumor necrosis (TNF) produces necrotic responses. At least some of the IFN-on macrophages in humans may be mediated by 1,25-dihydroxyvitamin D3. These findings highlights the complex involvement of cytokines in antimicrobial resistance, with IFN- playing a key role [17].

16. Nanotechnology against antibiotic resistance

Due to its favourable physico-chemical characteristics, the targeted efficacy of drugs, increased absorption and biodistribution, drug-based nanotechnology have attracted the attention of researchers and pharmaceutical companies.

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Efficiency drug loading of both lipophilic and hydrophilic antibiotics is enhanced by nano-sized particles, resulting in antibacterial activity.

In addition, the passage through the reticuloendothelial system allowed an improved uptake more anticipated cellularity of antibiotic-loaded nanosystems. nanosystem surface and zeta potential lead to interactions with proteins, tissues and various tissue components, altering biodistribution and cellular uptake. Host cells anionic, such as macrophages, attract positively charged nanosystems at the expense of uncharged and negatively charged ones. Nanoparticles produce lethal changes in shape and structure of bacterial cells; nanophotothermal treatment uses nanoparticles inorganics, such as AuNPs, to kill harmful bacterial cells [18].

17. Probiotics as a means of treating antimicrobial resistance

Probiotic products are living organisms that have a positive effect on the host, being mostly classified in the genera *Bifidobacterium* and *Lactobacillus*, but there are also strains of other species available on the market. The probiotic is carefully chosen so that it does not contribute to the spread of antibiotic resistance and not carry resistance genes that could be transmitted between people. Concomitant administration of antibiotics and probiotics has shown to reduce the severity, duration and frequency of antibiotic-associated diarrhoea. This encourages people to strictly adhere to antibiotic prescriptions, which slows down spreading resistance. The extent to which probiotics directly prevent the transmission of antibiotic resistance; however, maintaining a healthy microbiome during administration of antibiotics may provide opportunities for reducing the spread of resistance [19].

18. Medicinal plants used against antimicrobial resistance

Both infectious and non-infectious diseases are commonly treated using traditional herbal remedies. Instead, the antimicrobials used to treat bacterial infections caused by multi-drug resistant strains multidrug-resistant bacteria and total drug resistance are becoming increasingly common in clinical settings, and people are looking for new ways to treat such diseases. Herbal medicines are considered superior options for bacteria present and in the development of antimicrobial resistance, so that it expects to protect people against infection. Herbal antimicrobials work in a similar way to antibiotics in that they kill bacteria or limit their development. Similar to antibiotic resistance in microorganisms, resistance to herbal medicine may have mechanisms that are not yet fully understood.

Recent research on the antibacterial effects of medicinal plants on isolates clinical studies have revealed that some microorganisms are insensitive or resistant to several folk herbal antimicrobial components [20].

19. Conclusions

Alternatives to antibiotics, such as probiotics and lytic bacteriophages, can help reducing the global burden of antimicrobial resistance. Spreading antimicrobial resistance can be limited through rational use of antibiotics, infection control, immunisation, promotion of good practices in food supply and control person-to-person spread through screening, treatment, awareness raising and education. Nowadays, the World Health Organization is taking steps in the right direction because created a global antimicrobial resistance surveillance system that works with regional and national antimicrobial resistance surveillance systems to provide comprehensive and timely data. Similar efforts to resolve each of the different contributing factors would help lower the rate of resistance development globally.

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