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ANTIBIOTIC RESISTANCE BREAKERS; A REVIEW

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ABSTRACT

Antimicrobial resistance is the ability of a microbe to resist the effects of medication that once could successfully treat the microbe. Resistance to available antibiotics in pathogenic bacteria is currently a global challenge since the number of strains that are resistant to multiple types of antibiotics has increased dramatically each year and has spread worldwide. Infections of antibiotic-resistant pathogens pose an ever-increasing threat to mankind. To unlock this problem, the use of an 'antibiotic adjuvant' in combination with an antibiotic is now being exploited. This approach enable to prolong the lifespan of these life-saving drugs. This review provides an overview of the antibiotic adjuvants mainly the breakers of resistance, the basis of their operation and the remaining issues to be tackled in this field.

KEYWORDS: Resistance breakers, ESKAPE pathogens, Antibiotic potentiators, Beta-Lactamase inhibitors, Efflux pump inhibitors, Permeabilizers.

INTRODUCTION

ANTIMICROBIAL RESISTANCE

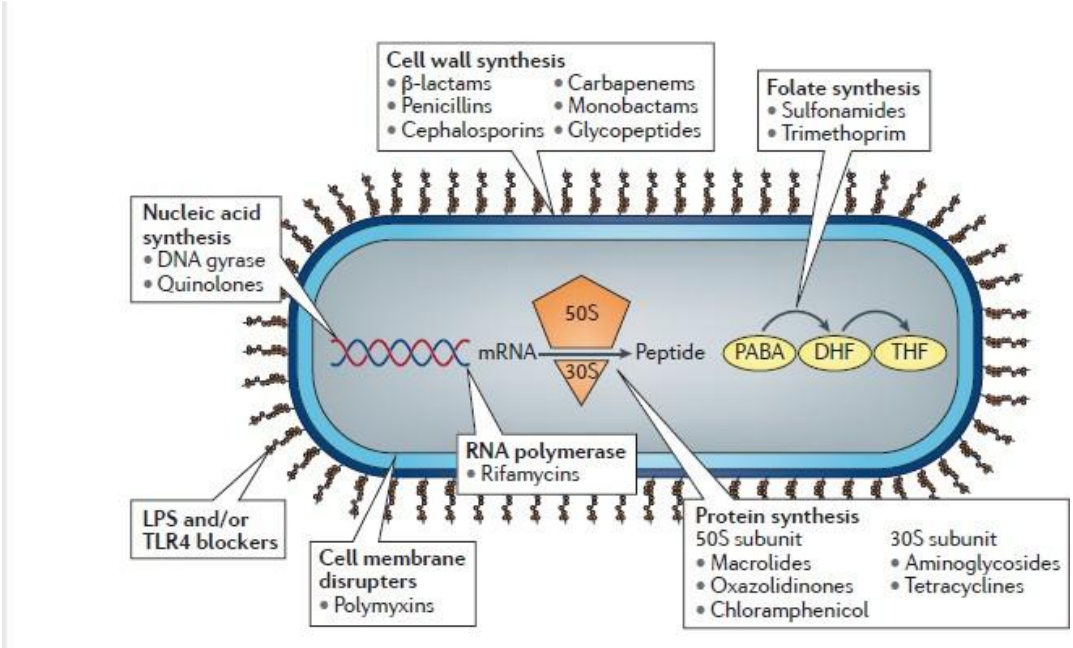
Resistance to current antibiotics is rapidly increasing. In the report of global antimicrobial resistance, the World Health Organization (WHO) portrayed high levels of antibiotic resistance in the bacteria that cause common infections.

The so-called ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) are especially important owing to their role in many infections in human organs (such as the lung and urinary tract), the frequency of antibiotic resistance amongst them and the lack of

alternative antibiotics. Several of these pathogens are Gram-negative bacteria, which are of particular concern as in these organisms resistance of up to 50% against carbapenems, the current last line of defence, has been reported in some developing countries1. A few new antibiotics against Gram-positive bacteria have become available in recent years, but no totally new class of antibiotic has been introduced for the treatment of Gram-negative infections for more than 40 years.

There are four main molecular mechanisms by which bacteria may resist the effects of antibiotics; modification of the target site, modification or destruction of the antibiotic, antibiotic efflux *via* efflux transporters and reduced antibiotic influx through decreased membrane permeability. These resistance mechanisms can be present together in different combinations in one bacterial cell, potentially allowing high level resistance to multiple antibiotic compounds simultaneously. Some bacteria possess an innate insensitivity towards certain classes of antibiotics (intrinsic resistance), either through naturally possessing any of the above mechanisms in the absence of artificial antibacterial selection pressure (ampicillin resistance in *Klebsiella* spp.), lack of the antibiotic target (vancomycin resistance in lactobacilli) or lack of a metabolic pathway or enzyme necessary for the activation of the drug (metronidazole resistance in aerobic bacteria) Resistance towards antibiotics is acquired by bacteria through either vertical evolution (endogenous) or horizontal evolution (exogenous). Vertical evolution involves the occurrence of a spontaneous mutation within the bacterial genome that confers on the bacterium (and subsequently its progeny) increased resistance to a given compound. The process to achieve high level resistance is often stepwise, wherein the selection pressure of antibiotic treatment causes an initial mutation that allows domination of the pathogen population by the mutant bacteria, followed by subsequent additional mutations that confer an additional survival advantage during further antibiotic therapy. Though mutation frequencies can often be as low as 10−8, this is offset by the vast numbers of cells in bacterial colonies (Drlica and Perlin 2011). Work by Santos Costa et al. into fluoroquinolone resistance in S. aureus showed that, in this case at least, an intermediate resistance phenotype (via upregulation of efflux pump expression) is first to appear and acts as a platform from which higher level resistancemutations can occur by ensuring a sub-lethal intracellular fluoroquinolone concentration.

Mechanism involving resistance



Antibiotics can be classified by their mechanism of action. Resistance to one antibiotic within a class can confer resistance to others with the same target. Resistance arises by two main mechanisms: random mutations during DNA replication and transfer of DNA between bacteria, often as plasmids. The transferred DNA can contain genes that confer resistance, and natural selection then favours the survival of the resistant bacteria during antibiotic treatment of a patient. DHF, dihydrofolic acid; LPS, lipopolysaccharide; PABA, para-aminobenzoic acid; THF, tetrahydrofolic acid; TLR4, Toll-like receptor 4.

The ways of breaking resistance to current antibiotics are found as soon as possible. One strategy to achieve this goal is to co-administer another drug with the failing antibiotic, which restores sufficient antibacterial activity. The use of such antibiotic resistance breakers (ARBs) to salvage antibiotics is exemplified by the long-standing, successful and widespread co-administration of β-lactamase inhibitors, such as clavulanic acid, with β-lactam antibiotics, such as amoxicillin. Resistance to amoxicillin and to this combination of drugs has been slow to emerge. However, mutation of the β- lactamase TEM1 — thought to be the greatest driver of resistance to this class of antibiotics — has now occurred owing to the selection of organisms with clavulanate-insensitive β-lactamases. As noted above, several new β-lactamase inhibitors offer the hope of counteracting resistance to β-lactam antibiotics in the near term, but further exploitation of β-lactamase inhibitors may be of limited use in the longer term, as there has been a 100-fold increase in the number of known β-lactamases in

the past 40 years11.

Surprisingly, the success of β-lactamase inhibitors has not led to substantial clinical and commercial exploitation of the concept of ARBs beyond this class. Attempts to reduce resistance by blocking efflux pumps on bacterial cells — which can diminish the effectiveness of antibiotics by lowering their intracellular concentration — have been pursued for many years, so far without notable success. However, efforts continue and deserve further attention. Novel combinations of existing classes of antibiotics could also be investigated; for example, macrolides may be able to synergize with β-lactams and fluoroquinolones.

Current studies focus on the identification of broad-spectrum ARBs by repurposing marketed drugs and nutraceuticals. ARBs selected from marketed drugs would be particularly useful as their development could be faster, cheaper and probably have a higher success rate than that for new molecules. This could be crucial, given the pressing need for strategies to tackle antibiotic resistance, the long development timelines for new antibiotics and the challenging financial environment for new antibiotic research and development. One ARB could potentially revitalize several antibiotics in a class11, and some ARBs may even work across classes. Lethal bacterial infections might be effectively treated with far fewer compounds than would be required to replace existing antibiotics. Moreover, the concept may help to extend the lifespan of future antibiotic classes. Here, after highlighting the priority bacteria, key antibiotics to be salvaged and the properties of ARBs, we discuss a list of proposed priority candidates for further investigation and issues for their development.

Modifying enzyme inhibitors

Bacteria employ a diverse range of enzymes to modify or destroy antibiotics in order to render them ineffective and achieve a resistant phenotype. These enzymes can be categorised by both their mechanisms of action and their substrate antibiotics. Hydrolysis of certain susceptible bonds within the antibiotic molecule, transfer of a functional group to the antibiotic and (less commonly) the actions of redox and lyase enzymes are all examples of detoxification mechanisms. This led to the development of antibiotics that would tolerate their actions, such as the *β*-lactam flucloxacillin which was designed to tolerate the action of the penicillinases. A method which has found more success is the design of modifying enzyme inhibitors, a term which encompasses the wide variety of chemical compounds that target bacterial enzymes involved in antibiotic modification and destruction. Modifying enzyme inhibitors are used to disrupt bacterial detoxification enzymes, increasing the

effectiveness of a co- administered antibiotic. Two major classes are the BLIs and aminoglycoside-modifying enzymes.

CONCLUSIONS

Several potential ARBs are available for β-lactam antibiotics (carbapenems, cephalosporins and penicillins), which is the most important class of antibiotic for the treatment of antibiotic-resistant Gram- negative bacteria. Several of these ARBs disrupt the bacterial cell wall, which contains polyanionic LPS and is stabilized by the cross-bridging of divalent cations122. Drugs that target these divalent cations destabilize the membrane, increase its permeability and allow access of molecules that were partially or fully excluded. Indeed, several polycation antibiotics — for example, polymyxins, aminoglycosides and dibasic macrolides such as azithromycin — act through this mechanism123 and these are ARBs them- selves when co-administered with β-lactam antibiotics. In addition to potentially salvaging our best Gram-negative antibiotics, this approach may also make 'Gram-positive antibiotics' useful against Gram-negative bacteria. Further careful screening of polycation molecules in the drug pharmacopeia may identify new ARBs of this type.

Additionally, there are regulatory considerations that need to be addressed (BOX 2). Will regulatory authorities require three-way clinical trials, comparing each drug individually with the combination? Do we have the time to perform such perfect clinical trials? The Ebola epidemic in West Africa has shown that society is now amenable to fast-track development of new drugs when a global emergency dictates it. Profit margins for combinations of known drugs may be low even if they are lifesavers.

Pharmaceutical or biotechnology companies are unlikely to invest in this approach, although those that currently sell antibiotics may be able to preserve sales and reach new patents by adding an ARB in a new combination. In particular, as no ARBs have been identified for fluoroquinolones to find ARBs for these antibiotics could be commercially viable if supported by 'method of use' patents (BOX 2). However, in general, unless a new economic model is developed for antibiotics, the development of ARBs will have to be pursued by government, public sector or philanthropic agencies, or combinations of these.

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