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Review

Breakthroughs in bacterial resistance mechanisms and the potential ways to combat them

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ABSTRACT

Multidrug-resistant (MDR) bacteria have increased at an alarming rate over recent decades and cause serious problems. The emergence of resistant infections caused by these bacteria has led to mortality and morbidity; consequently there is an urgent need to find solution for combating bacterial resistance. In the present paper, first, some mechanisms of antibiotic resistance such as changing the antibacterial agent's uptake and biofilm formation are discussed. Following, for removing the antibacterial resistance, a wide range of approaches like developing new generations of antibiotics, combination therapy, natural antibacterial substances and applying nanoparticulate systems have been explained. Among them, antibiotic delivery via nanoparticles, has been attracted more attention recently, so discussed in present review, separately.

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1. Introduction

In recent years, bacterial resistant infections have become a global health challenge and threaten health of societies [1–3]. Due to emergence of resistant infections, existing antibacterial drugs have become less effective or even ineffective; this has led to development of new antibacterial drugs. In this context, mentioning two points seems to be necessary; first, the structural and antimicrobial mechanism similarities with the old ones have raised the concern that bacteria may rapidly develop resistance to them after clinical use. Second, research on treatments to replace antibacterial drugs is still in the early stages. Consequently, it is essential to reduce the emergence of resistant bacteria to maintain the efficacy of existing drugs for treating the common and life-threatening infections.

Understanding bacterial resistance mechanisms helps us to find the adequate therapeutics. These are included antibiotic efflux, antibiotic inactivation, and biofilm formation and target modification.

Various approaches have been developed and used to eradicate antibiotic resistance. Novel antimicrobial discovery and combination antibiotic therapy are being pursued in order to combat emerging antibiotic resistant bacteria [4,5]. Combination therapy reduces the adverse effects of antibiotics and increases the potency of antimicrobial agents against resistant pathogens [6]. Many research groups are studying the effects of natural antimicrobial substances on hard-to-treat bacteria. These agents can be used as stand-alone or adjunctive therapies. Phenolic compounds such as catechins are increasingly attracting attention [7]. Improving the antibiotic efficacy against bacteria can also be enhanced by applying novel drug delivery systems. Nanoparticles such as solid lipid nanoparticles, liposomes and nanoemulsions are considered therapeutic agent delivery systems [8].

2. Problems associated with antimicrobial resistance

Antibiotic resistance can occur in both hospital and community settings and leads to emergence of resistant pathogens. Community-associated infections have been an important source of morbidity and death of patients [2,9]. The emergence of nosocomial or health care associated infections is a public health problem which is life threatening. These kinds of infections affect many people around the world and only in the USA antibiotic-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* cause ~19,000 deaths per year [10]. Some common resistant bacteria are summarized in Table 1.

Some resistant pathogens are resistant to more than one class of antimicrobial agents. These multidrug resistant (MDR) species have become cause for serious concern, particularly in hospitals and other healthcare institutions. Some of the most problematic MDR organisms are *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli* and *Klebsiella pneumoniae* bearing extended-spectrum β-lactamases (ESBL), Vancomycin-resistant enterococci (VRE) and MRSA [18,19].

Understanding mechanisms of bacterial resistance might be helpful to know how to manage recalcitrant infections.

3. Mechanisms of antimicrobial resistance

Bacterial resistance to antibiotics can be divided into two types: I) intrinsic or innate resistance and II) acquired resistance. The first one is a feature of a particular bacterium and depends on its biological properties (*E. coli* shows intrinsic resistance to vancomycin). Acquired resistance results from: I) acquisition of resistance genes by bacteria, II) mutation of chromosomal DNA, III) combination of both mechanisms.

Regulatory genes controlling multi-drug resistance and bacterial biofilm formation also play important roles in antibacterial resistance. Some important forms of antibacterial resistance are illustrated in Fig. 1 and explained in the following sections.

3.1. Molecular basis of antimicrobial resistance

Acquisition of resistance genes can be mediated by transferable genetic elements such as plasmids, transposons and integrons; notably, transmissible plasmids are a highly efficient means for horizontal gene transfer through a process called conjugation. During this procedure, the cell surface of both donor and recipient bacteria come into contact to form a bridge to transfer conjugative plasmids from the donor bacteria to the recipient one [20].

Plasmid-mediated antibiotic resistance in bacteria is frequently observed. For example, in *Enterobacteriaceae*, quinolones and β-lactams are used as first-line antibiotics for treatment. While the prevalence of plasmid-mediated quinolone resistance and plasmid-encoded β-lactamases is now observed and regularly increasing [21]. Another example of this type of resistance is vancomycin resistance in enterococci. Enterococcal species have been a major health problem around the world, as they are resistant to multiple antibiotics [22]. The TN1546 transposons located on plasmids transferred horizontally among enterococcal populations spreading

Table 1
Antibiotic resistant bacteria commonly associated with infections in hospitals and in the community.

Bacteria	Examples of typical diseases	Resistant to	Mechanisms of resistance	Ref.
Escherichia coli	Urinary tract infections, blood stream infections	3rd gen. cephalosporins, Fluoroquinolones	Over expression of a TEM or *ampC* β-lactamase	[11]
Staphylococcus aureus	Wound infections, blood stream infections	Oxacillin, vancomycin, linezolid	Alteration of target sites in the cell wall of *Staphylococcus aureus*	[12]
Streptococcus pneumoniae	Pneumonia, meningitis, otitis	non-susceptible or resistant to penicillin	Alteration of penicillin-binding proteins (PBPs) affinity to the antibiotic	[13]
Shigella species	Diarrhea (“bacillary dysenteria”)	Fluoroquinolones	Mutations in *acrA-tolC* genes	[14]
Klebsiella penumoniae	Pneumonia, blood stream infections, urinary tract infections	3rd gen. cephalosporins 3rd carbapenems	Loss of porin	[15]
Neisseria gonorrhea	Gonorrhea	3rd gen. cephalosporins	Chromosomal mutations	[16]
Vancomycin-resistant enterococci	Urinary tract infections, wound infections and intraabdominal infections	Vancomycin	Over expression of *VAN A* and *VAN B*	[17]