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Nanotechnology as a therapeutic tool to combat microbial resistance ☆

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ABSTRACT

Use of nanoparticles is among the most promising strategies to overcome microbial drug resistance. This review article consists of three parts. The first part discusses the epidemiology of microbial drug resistance. The second part describes mechanisms of drug resistance used by microbes. The third part explains how nanoparticles can overcome this resistance, including the following: Nitric oxide-releasing nanoparticles (NO NPs), chitosan-containing nanoparticles (chitosan NPs), and metal-containing nanoparticles all use multiple mechanisms simultaneously to combat microbes, thereby making development of resistance to these nanoparticles unlikely. Packaging multiple antimicrobial agents within the same nanoparticle also makes development of resistance unlikely. Nanoparticles can overcome existing drug resistance mechanisms, including decreased uptake and increased efflux of drug from the microbial cell, biofilm formation, and intracellular bacteria. Finally, nanoparticles can target antimicrobial agents to the site of infection, so that higher doses of drug are given at the infected site, thereby overcoming resistance.

Contents

Abbreviations: NP, nanoparticle; NO NP, nitric oxide-releasing nanoparticle; chitosan NP, chitosan-containing nanoparticle; PPNG, penicillin-resistant *Neisseria gonorrhoeae*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; MIC, minimum inhibitory concentration; MFS, major facilitator superfamily; SMR, small multidrug resistance family; RND, resistance nodulation cell division family; PBP, penicillin binding protein; VRE, vancomycin-resistant *Enterococcus*; VRSA, vancomycin-resistant *Staphylococcus aureus*; Erm, erythromycin resistance methylase; NDM-1, New Delhi metallo beta-lactamase 1; VatD, virginiamycin acetyltransferase; PABA, para-aminobenzoic acid; TA genes, toxin–antitoxin genes; EPS, extracellular polymeric substance; RNOS, reactive nitrogen oxide intermediates; O_2-, superoxide; $OONO-$, peroxynitrite; NO_2, nitrogen dioxide; N_2O_3, dinitrogen trioxide; H_2O_2, hydrogen peroxide; NOS, nitric oxide synthetase; RSNO, S-nitrosothiol; MIC90, minimum inhibitory concentration; CFU, colony forming unit; MRAB, multidrug-resistant *Acinetobacter baumannii*; GSH, glutathione; NO NP/GSH, mixture of hydrogel/glass composite NO NPs with glutathione (GSH) in aqueous solution; GSNO, S-nitrosoglutathione; LPS, lipopolysaccharide; Ag, silver; Zn, zinc; Cu, copper; Ti, titanium; Mg, magnesium; Au, gold; Bi NP, bismuth-containing nanoparticle; Al_2O_3 NP, aluminum oxide-containing nanoparticle; Ag NP, silver-containing nanoparticle; ROS, reactive oxygen species; SCC, silver carbene complex; HIV 1, human immunodeficiency virus type 1; HBV, Hepatitis B virus; ZnO NP, zinc oxide-containing nanoparticle; PVA, polyvinyl alcohol; CuO NP, copper oxide-containing nanoparticle; TiO_2 NP, titanium dioxide-containing nanoparticle; .OH, hydroxyl radical; MgX_2 NP, magnesium halogen-containing nanoparticle; MgO NP, magnesium oxide-containing nanoparticle; Au NP, gold-containing nanoparticle; Au NP-AMP, gold-containing nanoparticle with ampicillin bound to its surface; Bi NP, bismuth-containing nanoparticle; MDR, multidrug resistant; Al_2O_3 NP, aluminum oxide-containing nanoparticle; Au@Van NP, gold-containing nanoparticle capped with vancomycin; chitosan–alginate NP, chitosan–alginate nanoparticle; chitosan–Ag NP, silver-containing nanoparticle which also contains chitosan; TiO_2–Ag NP, nanoparticles containing both TiO_2 and Ag; MBC, minimum bactericidal concentration; QAC, quaternary ammonium compound; TFC, thin film composite; zero-valent Bi NP, nanoparticle containing zero-valent Bi; SPION, superparamagnetic iron oxide NP; Fe_3O_4, magnetite; MPS, mononuclear phagocyte system; LTP NP, L-tyrosine polyphosphate nanoparticle.

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1. Introduction

For many years, antimicrobial drugs have been used to inhibit or kill bacteria and other microbes. However, microbial resistance to these drugs has developed on a very large scale over time, greatly reducing their effectiveness, and is an ever growing problem [1]. One of the most promising strategies for overcoming microbial resistance is the use of nanoparticles.

This review article consists of three parts: The first part discusses the epidemiology of microbial resistance. The second part discusses development of resistance and specific mechanisms of resistance [1]. These include, among others, decreased uptake and increased efflux of drug from the bacterial cell [2]; expression of resistance genes that code for an altered version of the substrate to which the antimicrobial agent binds [3,4]; and covalent modification of the antibiotic molecule which inactivates its antimicrobial activity [2]. In addition, bacteria can avoid contact with antibiotics by forming biofilms and by intracellular activity [5,6,2].

The third part of this review discusses mechanisms by which nanoparticles combat microbial resistance. Several types of nanoparticles use multiple mechanisms simultaneously to combat microbes, including nitric oxide-releasing nanoparticles (NO NPs), chitosan-containing nanoparticles (chitosan NPs), and metal-containing nanoparticles. The use of multiple simultaneous mechanisms of antimicrobial action makes the development of resistance to these nanoparticles unlikely, because multiple simultaneous gene mutations in the same microbial cell would be required for that resistance to develop [7,5,8,6,9]. It is also possible to package multiple antimicrobial agents within the same nanoparticle [10,5]. Development of resistance to the multiple antimicrobial agents within these nanoparticles is, again, unlikely [11], possibly because it would require multiple simultaneous gene mutations in the same microbial cell. Nanoparticles can also overcome drug resistance mechanisms of microbes, including decreased uptake and increased efflux of drug from the microbial cell [10,12,6], biofilm formation [1,6], and intracellular bacteria [5,12,6]. Finally, nanoparticles have been used to target antimicrobial agents to the site of infection, so that higher doses of drug can be given at the infected site, thereby overcoming resistance with fewer adverse effects upon the patient [13].

2. Epidemiology of antimicrobial resistance

Over the years, resistance to antimicrobial drugs has become increasingly widespread, and this has resulted in a significant threat to public health [1]. The long list of drug-resistant bacteria includes sulfonamide-resistant, penicillin-resistant, methicillin-resistant, and vancomycin-resistant *Staphylococcus aureus*, macrolide-resistant *Streptococcus pyogenes*, penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant *Enterococcus*, multidrug-resistant *Mycobacterium tuberculosis*, penicillin-resistant *Neisseria gonorrhoeae* (PPNG), *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Shigella flexneri*, *Salmonella enterica*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Vibrio cholerae*, and beta-lactamase-expressing *Haemophilus influenzae* [14–17]. 40–60% of strains of *S. aureus* found in hospitals in the United States and United Kingdom are resistant to methicillin (MRSA), and most of these strains are also resistant to multiple antibiotics [16].

Bacterial drug resistance has numerous negative effects upon medicine and society. Drug-resistant bacterial infections result in higher doses of drugs, addition of treatments with higher toxicity, longer hospital stays, and increased mortality [6,15]. Methicillin-resistant *S. aureus* (MRSA) is associated with more deaths than methicillin-sensitive *S. aureus* (MSSA) [16]. In the United States, infections due to antibiotic-resistant bacteria add $20 billion to total health care costs plus $35 billion in costs to society [15].

3. Mechanisms of resistance of microbes to antimicrobial drugs

3.1. Development of resistance to antimicrobial drugs

Development of drug resistance occurs in (at least) three steps: Acquisition by microbes of resistance genes, followed by expression of those resistance genes, followed by selection for microbes expressing those resistance genes. First, bacteria acquire resistance to single and multiple drugs through horizontal gene transfer by transformation, conjugation, and transduction [1]. Bacteria can also acquire resistance genes by spontaneous mutation of existing genes [18]. Multiple drug resistance is acquired when a bacterial cell already containing one type of drug resistance gene acquires another type of drug resistance gene [1,2]. Second, in response to exposure to antimicrobial drug, microbes express the resistance gene [2]. Third, resistance becomes widespread when there is selection for microbes that express resistance genes against the antimicrobial drug. This selective pressure in favor of resistance occurs whenever microbes are exposed to the drug but not eradicated (either by the microbicidal effects of the drug itself, or by microbistatic effects of the drug followed by killing by the host's immune system) [1].

In any setting that creates this selective pressure in favor of drug resistance (such as poor patient compliance, or use of a time-dependent antibiotic with long half-life), the likelihood of that resistance actually developing is increased by longer duration of use of the antimicrobial drug [2]. In addition, microbistatic drugs, which inhibit but do not kill microbes, are more likely than microbicidal drugs to allow some