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Interaction of copper oxide nanoparticles with bacterial nucleic acids: a mini-review

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ABSTRACT

Despite the wide use of conventional antibiotics to treat bacterial infections, bacteria have now become resistant to many antibiotics and other antibacterial agents. This resistance is heritable and allows the spread of intractable bacterial infections, which is one of the biggest health challenges encountered around the world. This issue has led to the search for new therapeutic antibacterial agents. In the last few decades, nanomaterials, especially metal and metal oxide nanoparticles (NPs), have gained much attention due to their advantageous properties, including large surface-to-volume ratio and high antimicrobial activity. Among various metal and metal oxide NPs, copper oxide NPs have been particularly investigated owing to their biocompatibility and antibacterial activity against both Gram-positive and Gram-negative bacteria. Several antibacterial mechanisms have been proposed for copper oxide NPs, among which their interaction with bacterial deoxyribonucleic acid and ribonucleic acid is considered important. These NPs can disrupt the accuracy of DNA replication by changing the DNA sequence which result in differences in the target sequences bound by random amplification of polymorphic DNA (RAPD) primers. This mini-review discusses this interaction according to recent studies.

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Introduction

Microbial infections have become serious medical problems, especially in immunocompromised patients, because of the failure of conventional antibiotics against multidrug-resistant bacteria [1-3]. A variety of organic and inorganic nanomaterials have been investigated as an alternative to conventional antibiotics based on their unique properties such as a higher surface-to-volume ratio (SA:V) compared to bulk materials [4]. In addition, these nanomaterials can be classified in three-dimensional (3D), two-dimensional (2D), one-dimensional (1D), and zero-dimensional (0D). Some antimicrobial nanoparticles (NPs) as zero-dimensional nanomaterials can control contamination in the laboratory environment, and kill bacteria in living cells [5-7]. Antimicrobial NPs are more stable and can be stored for a longer time compared to most antibiotics [8, 9]. NPs can withstand adverse conditions such as high sterilization temperatures, which can inactivate conventional antibiotics [10, 11]. Moreover, nanomaterials can be used in the delivery of conventional antibiotics with several advantages: I) they can have a uniform shape and good distribution in the target tissue; II) improved solubility of insoluble drugs; III) the possibility of controlled and stimulus-responsive drug release [12, 13]. Among metal and metal oxide NPs, increasing attention in both therapeutic and industrial fields is being paid to copper or copper oxide NPs [14, 15]. These inexpensive NPs have been proposed, instead of more expensive metal NPs (gold, platinum, or silver), for micro-electrical applications, antibacterial materials in the textile industry, water disinfection, food packaging, and in medical applications to prevent infections [16]. Moreover, in contrast to conventional chemical disinfectants, copper oxide NPs are not expected to produce any harmful environmental pollution [15, 17, 18].

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Small-size NPs may be functionalized with natural bioactive compounds isolated from medicinal plants, fungi, alga, lichens, and bacteria to increase their antimicrobial activity [19, 20]. Many studies have investigated the antimicrobial activity of NPs against human pathogenic bacteria, such as *Escherichia coli* (Gram-negative) and *Staphylococcus aureus* (Gram-positive) [21, 22]. The formation of biofilms by bacteria is known to be another important cause of resistance, because it protects bacteria against antibiotics, and is one of the main causes of chronic infections [23, 24]. Electrostatic interactions between NPs and biofilms can affect how they react with each other [25, 26]. Copper oxide NPs (CuONPs) are a good example of antibacterial nanomaterials. CuONPs can affect biological macromolecules, including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), as well as proteins and other structural components of bacterial cells [27].

Interaction of CuO NPs with DNA and RNA

NPs can attach to the bacterial membrane through electrostatic interactions, interfering with membrane components, and can even cause destruction of the bacterial membrane [28]. The amine and carboxyl groups of the peptidoglycan layer are functional groups in the bacterial cell wall, which mainly react with copper or copper oxide. This interaction can cause damage to the cell wall, which is an antimicrobial mechanism of many different types of NPs [29]. However, the mechanism of antibacterial activity displayed by CuONPs is not fully understood. Nevertheless, the amount of copper ion release from the NPs, and the subsequent generation of reactive oxygen species (ROS) is assumed to be the main reason [30]. Both these mechanisms (Cu ion release and ROS production) can prevent DNA replication and inhibit protein synthesis in bacteria and therefore provide antimicrobial activity, and can also overcome antibiotic resistance in bacteria (Figure 1) [31, 32].

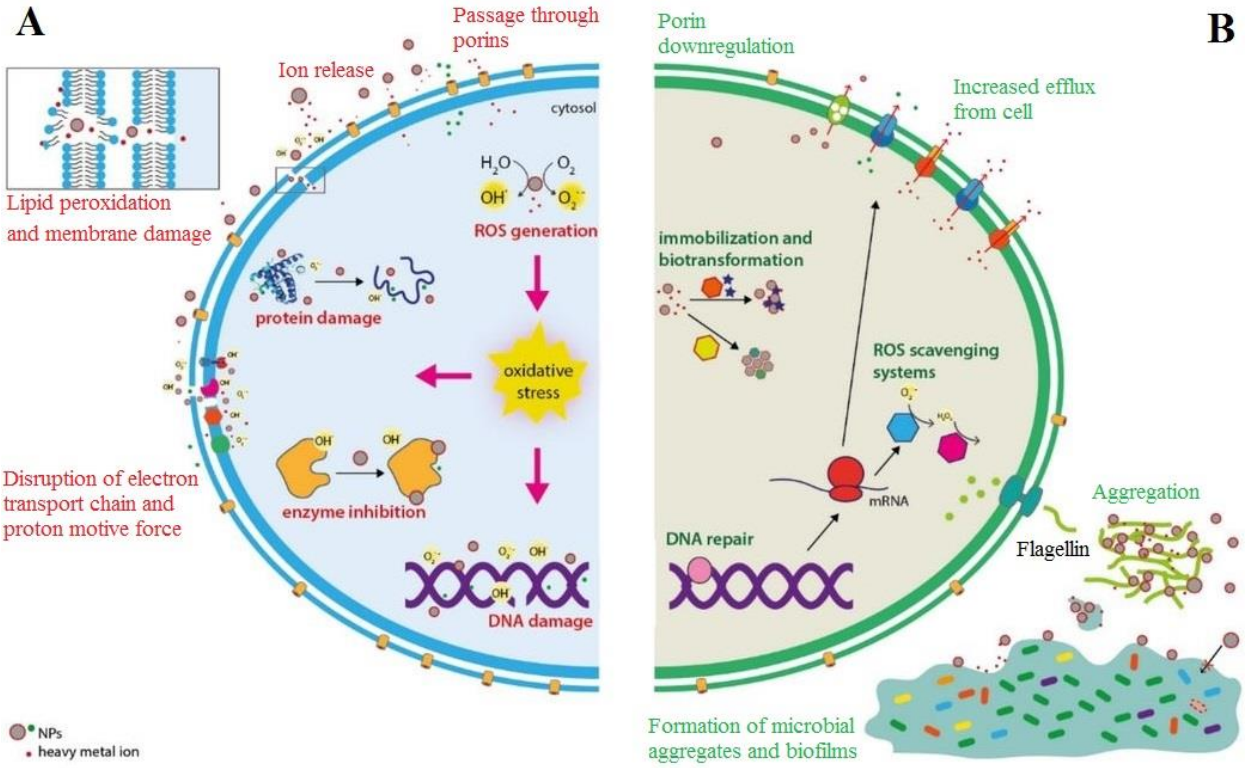

Fig. 1. The main mechanisms for **(**A) antibacterial activity of metal or metal oxide NPs (including CuONPs); (B) possible resistance responses in bacteria (adopted with modification from [32]).

Copper oxide NPs probably disrupt the accuracy of DNA replication. The evidence for this assertion relies on changes in the DNA sequence that lead to differences in the target sequences bound by random amplification of polymorphic DNA (RAPD) primers [33, 34]. CuONPs can also induce breaks in single-stranded DNA and affect gene expression [35-37]. CuONPs caused extensive changes to the chromosomal DNA structure of the bacteria, involving breaks in the DNA structure, and since these fragments

were created randomly, many of the fragments were not detected by the primers and were therefore not amplified [38]. NPs also cause disrupt genes that control transcription and replication mechanisms in bacteria [39]. The activity and base sequence of the gene promoters are also affected by NPs, and NPs can affect the ability of RNA polymerase to open the nucleic acid helix and carry out transcription. In fact, any factor that damages DNA can basically cause the death of bacteria [40]. The production of ROS resulted from direct and indirect interaction (releasing metal ions of metal ore metal oxide NPs such as AgNPs can impact the reduced nicotinamide adenine dinucleotide phosphate (NADPH) production-related gene, antioxidant genes, and oxidative stress-related genes [41]. Moreover, the size of the NPs can determine the level of genotoxicity. As smaller ones can produce more ROS and higher genotoxicity compared to larger ones [42].

Conclusions

The main antibacterial mechanism of CuONPs involves mediating damage to cell lipids, proteins, RNA, and DNA either by direct binding or by ROS generation followed by oxidation reactions. The production of ROS caused by direct and indirect interaction of these NPs may change the expression of the NADPH production-related gene, oxidative stress-related genes, and antioxidant genes. Additionally, the genotoxicity of CuONPs can be increased by decreasing their size. To mitigate the antibacterial effects caused by a low concentration of CuONPs, bacteria can over-express metal ion efflux systems, increase antioxidant activity, reduce metal entry into the cell by down-regulation of porins, or up-regulate DNA repair systems. At higher doses of CuONPs, morphology changes are followed by major disruption of biological macromolecules, specifically lipids, proteins, and nucleic acids. Therefore, choosing an effective dose of CuONPs is a critical factor to obtain desirable antibacterial activity against Gram-negative and Gram-positive bacteria, without damaging surrounding host tissue or polluting the environment.

Study Highlights

- The antibacterial mechanism of CuONPs involves mediating damage to cell lipids, proteins, RNA, and DNA either by direct binding or by ROS generation followed by oxidation reactions.
- The production of ROS caused by direct and indirect interaction of these NPs may change the expression of the NADPH production-related gene, oxidative stress-related genes, and antioxidant genes.
- The genotoxicity of CuONPs can be increased by decreasing their size.
- At higher doses of CuONPs, morphology changes are followed by major disruption of biological macromolecules, specifically lipids, proteins, and nucleic acids.
- Choosing an effective dose of CuONPs is a critical factor to obtain desirable antibacterial activity against Gram-negative and Gram-positive bacteria, without damaging surrounding host tissue or polluting the environment.

Abbreviations

DNA: Deoxyribonucleic acid
NADPH: The reduced nicotinamide adenine dinucleotide phosphate
NPs: Nanoparticles
RAPD: Random amplification of polymorphic DNA
RNA: Ribonucleic acid
ROS: Reactive oxygen species
(SA:V): Surface-to-volume ratio

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Authors' contribution

MA: conceptualization, preparing the first draft, and MRH: revising the manuscript.

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