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Review

Antimicrobial silver nanomaterials

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ABSTRACT

Antibiotic resistance is considered as one of the greatest health threats worldwide, and we are in a staring competition with microbes as antibiotic resistance mounts faster than our current rate of developing new and effective antibiotics. Therefore, newer metal-based antimicrobial agents with easily tuned physicochemical properties have been developed to fight against these antibiotic resistant bacteria. In this review, we begin with describing the mode of action of silver nanoparticles (Ag NPs) in damaging the bacterial extracellular membrane and their intracellular components that allows them to exhibit wide spectrum antimicrobial effect. The review also contains our insights on understanding not only the correlation between the NPs' physicochemical properties and their bactericidal mode of action but also the possible strategies to tune these physicochemical properties to optimize their bactericidal properties. The second focus of this review is on the emerging and highly efficient antimicrobial agents, ultrasmall Ag nanoclusters (Ag NCs). Ag NCs are ultrasmall NPs with core sizes less than 2 nm, and they contain "countable" Ag atoms as the core, which is protected by a certain number of organic ligands. The atomically precise property of Ag NCs provides a good platform to design and manipulate Ag NCs at atomic level to achieve optimized antimicrobial efficacy, which also favor the antimicrobial mechanism study.

Contents

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1. Introduction

Antibiotic resistance is considered as one of the greatest health threats by the World Health Organization (WHO) [1,2]. The first case of bacterial resistance could be traced back to 1967 in which penicillin resistant *Streptococcus pneumoniae* (*S. pneumonia*) was reported in Australia. In 1995, penicillin resistance was recorded for 23.6% of total *S. pneumoniae* isolates found in the US, and by 2000, this number has reached 85% of total *S. pneumoniae* isolates [3]. To date, the resistance is neither restricted to a certain bacteria strain nor against a specific antibiotic. Centers for Disease Control and Prevention (CDC) recorded that more than 70% of all bacterial causing infections could resist at least one of the main antimicrobial agents currently used in the clinic [4,5]. Moreover, antibiotic resistance is not an isolated problem of any particular country. Global surveillance data collected by WHO identified approximately 79% of bacteria have developed resistance to one or more antibiotics [6]. Each year, in the US alone, more than 2 million cases of illness and 23,000 deaths are attributed to these antibiotic resistant bacteria and the numbers are expected to be increasing over the years [7]. Similarly, it has been estimated that each year close to 25,000 people in Europe and 700,000 people worldwide die due to drug resistant bacterial infections [8,9]. The other real impact due to antibiotic resistance is not only limited to the increase in the complication risks and mortality rates, but also includes the increase in the healthcare cost. This antibiotic resistance has been estimated to rake over $20 billion in healthcare cost per year (and close to $35 billion cost for productivity) in the US [4]. Undoubtedly, the ideal solution to this antibiotic resistance problem would be the development of new classes of antibiotics in this arms race with bacterial evolution. Nevertheless, new antibiotics usually take decades to develop, making it impossible to curtail this pressing antibacterial resistance problem any time soon. In addition, it is a costly process and the new antibiotics will only be effective for a limited time before the inevitable resistance sets in again. This has economically inhibited pharmaceutical companies from developing new classes of antibiotics [10,11]. As such, there is an urgent need to develop an alternative antimicrobial agent that is cost-effective and powerful enough to be ahead of the bacterial evolution.

Metals like silver (Ag), copper (Cu), zinc (Zn), and magnesium (Mg) have been used to treat diseases long before the pharmaceutical antibiotic revolution. In addition, there is no single bacterial adaptation strategy that could provide them with universal resistance to all these metals, suggesting even if one antimicrobial metal failed, other metallic-based antibiotics could step in and fill in the gap [12,13]. More importantly, in the wake of nanotechnology advancement, material scientists could control the physicochemical properties of these metal nanomaterials to produce effective antimicrobial agents without exerting toxicity to the human patient [14,15]. Taking these into consideration, antimicrobial metal nanoparticles (NPs) could be the solution to the pressing antimicrobial resistance that we are now facing. To date, a new class of 'nanometallo-antibiotics' consisting of numerous metal NPs have been produced and investigated for their antimicrobial properties [16–18]. This review discusses one of the most promising nanometallo-antibiotics, Ag nanomaterials. These Ag nanomaterials have been well-developed in the field for the past two decades, and their effectiveness as antimicrobial agents has been well-documented in the literature. In addition, a number of efficient synthetic strategies have been recently developed toward achieving Ag nanomaterials with well-defined (and controlled) attributes and physicochemical features [19–27]. Despite the wealth of information on the Ag NPs' physicochemical features and the NPs antimicrobial activities, the link between these issues is not clearly elucidated. Hence, the discussions present in this review will focus on understanding the role of Ag NPs' physicochemical properties in determining their antimicrobial efficacy.

In this review, we begin with describing the Ag NPs' mode of action in damaging the bacterial extracellular membrane and their intracellular components, allowing these NPs to exhibit wide spectrum antimicrobial effect. The review also contains our insights on understanding not only the correlation of these physicochemical properties to the Ag NPs' bactericidal mode of action but also the possible strategies to tune the Ag NPs' physicochemical properties to optimize their bactericidal properties. With this understanding, we hope to provide a mechanistic framework to further tune the Ag NPs' antimicrobial efficacy, giving the next generation Ag NPs a fighting chance in overcoming the continually evolving resistance of microbial pathogens. In-depth and detailed mechanistic discussions of the anti-bactericidal mode of action can be found elsewhere [12]. Although human toxicity is an integral part in assessing the application of Ag NPs as antimicrobial agents, we would like to refer the readers to other recent reviews on the related topic [28–30].

As the physicochemical properties of any NPs would dictate the initial interactions with cells, the ability to tune the NPs' physicochemical properties with high precision is therefore a big advantage in deciphering the nanometallo-antibiotics effects on bacteria. Emerging over the horizon of the synthesis control of Ag NPs are atomically precise Ag nanoclusters (or NCs at atomic precision). Ag NCs are ultrasmall NPs with core sizes less than 2 nm, and they contain "countable" Ag atoms as the core, which is protected by a certain number of organic ligands. Ag NCs hold discrete electronic states and molecular-like properties, such as well-defined molecular structure, quantized charging, HOMO–LUMO transitions, molecular magnetism, molecular chirality, and strong luminescence [31–41]. In particular, Ag NCs show distinctly different physicochemical properties from their larger counterparts, the Ag NPs (particle size above 3 nm). Those unique physicochemical properties would increase the acceptance of Ag NCs in many biomedical applications, such as bioimaging, biosensing, and antimicrobial agents [42–50]. For example, Ag NCs feature with highly tunable antimicrobial efficiency that could be attributed to their unique and tailorable physicochemical properties, including ultrasmall size (high surface to volume ratio) and tunable Ag atoms and surface ligands per Ag NC. The discussion on the design and working mechanisms of Ag (and also gold (Au)) NCs-based antimicrobial agents forms the second focus of this review article.

2. Damages to bacterial membrane

Ag NPs could interact with the bacterial membrane, leading to bacterial membrane damage, which would subsequently kill the bacteria. Ag NPs would first accumulate on the surface of bacterial membrane, penetrate into the bacteria, and finally change the permeability of bacterial membrane, causing a substantial damage of the membrane [51]. Therefore, Ag NPs' physiochemical properties that could facilitate the interaction between Ag NPs and the bacterial membrane would become important to influence these NPs capability to invoke bacterial damage. These parameters of Ag NPs include size, shape, and surface. In particular, it was found that Ag NPs featuring with small sizes, (1 1 1) facets, and certain protecting ligand layers could better interact with the bacteria, resulting in high efficacy in damaging the bacterial membrane.

2.1. Membrane damage mechanism

In terms of working mechanisms of Ag NPs, as illustrated in Fig. 1a, the Ag NPs begin with a tight attachment and accumulation