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Review

Antibacterial applications of graphene oxides: structure-activity relationships, molecular initiating events and biosafety

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ABSTRACT

Bacterial infections may lead to diverse acute or chronic diseases (e.g., inflammation, sepsis and cancer). New antibiotics against bacteria are rarely discovered in recent years, which necessitates the exploration of new antibacterial agents. Engineered nanomaterials (ENMs) have been extensively studied for antibacterial use because of their long lasting killing effects in wide spectra of bacteria. Graphene oxide (GO) is one of the most widely studied ENMs and exhibit strong bactericidal effects. The physicochemical properties of GO play important roles in bacterial killing by triggering a cascade of toxic events. Many studies have explored the signaling pathways of GO in bacteria. Although molecular initiating events (MIEs) of GO in bacteria dominate its killing efficiency as well as toxicity mechanisms, they have been rarely reviewed. In this report, we discussed the structure–activity relationships (SARs) involved in GO-induced bacterial killing and the MIEs including redox reaction with biomolecules, mechanical destruction of membranes and catalysis of extracellular metabolites. Furthermore, we summarized the clinical or commercial applications of GO-based antibacterial products and discussed their biosafety in mammal. Finally, we reviewed the remaining challenges in GO for antibacterial applications, which may offer new insights for the development of nano antibacterial studies.

1. Introduction

Bacterial infection has been considered as one of the greatest threats to human health [1], because the wide uses of antibiotics have led to the increasing spread of multidrug resistant bacteria (a. k. a., superbugs) [2]. In addition, biofilm formation is another major hurdle that affects the bacterial killing efficiency of traditional antibiotics [3]. Despite these crises, the discovery of new antibiotics has significantly reduced during the past few years [4], which necessitates the exploration of new antibacterial agents.

The development of engineered nanomaterials (ENMs) provides opportunities to design a new generation of antibacterial agents as an alternative to antibiotics [5]. To date, ENMs including CuO [5], graphene oxide (GO) [6], Ag [7], ZnO [8], have been reported to show bactericidal effects against broad spectra of Gram-positive and Gram-negative bacteria. Compared to antibiotics, nano antibacterial agents exhibit two advantages: (1) ENMs are able to kill bacteria by multiple mechanisms (Fig. 1), including oxidative stress response, destruction of bacterial membrane, and interaction with cytosolic molecules; (2) ENMs exhibit long lasting bactericidal effects in the prevention of bacterial growth on the surfaces of solid substrates (e.g., paper, water filtration membrane, skin, etc.) owing to their extraordinary stability [6]. Among these nano antibacterial agents, GO has unique two dimensional (2D) honeycombed hydrophobic plane structure and hydrophilic groups including carboxylic (–COOH) and hydroxyl (–OH) groups on its edge [9]. This amphipathic structure of GO nanosheets could well facilitate their interactions with biomolecules including lipids, proteins, DNA, etc., and induce bacterial death without intracellular process. In contrast, some metal-based antibacterial nanoparticles (e.g., Ag) could dissolve in biological media and the released metal ions would diffuse into cytoplasm for bacterial killing. The physicochemical properties of GO have been demonstrated to play an important role in bacterial killing by triggering a cascade of toxic events [10,11]. The downstream signals as well as bacterial killing efficiency were significantly influenced by the molecular initiating events (MIEs) that reflect the initial interactions between GO and biomolecules in bacteria. Although different mechanisms including nano-knife, oxidative stress, membrane disruption, have been

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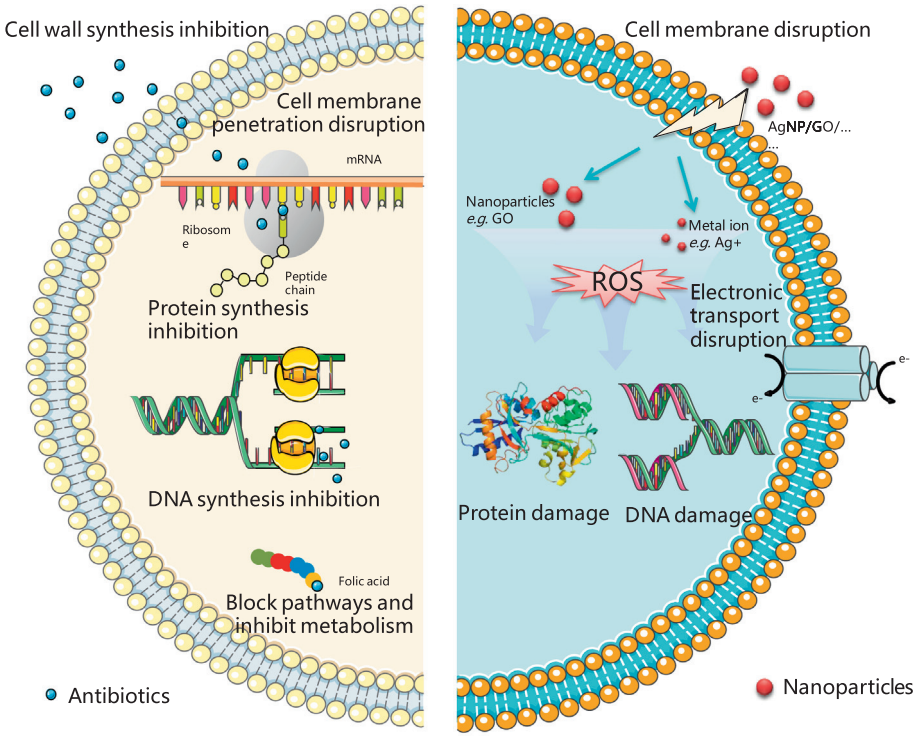

Fig. 1. (Color online) Comparison of bacterial killing mechanisms between antibiotics and ENMs. Antibiotics could prevent bacteria growth by inhibiting the synthesis of target biomolecules in bacteria, including cell walls, DNA, proteins, etc. In contrast, nanoparticles (e.g., AgNP, GO) could prevent bacterial growth by deconstruction of cell wall/membrane, interaction with DNA and proteins, and disruption of electron transport as well as the redox state in bacteria.

reported in GO-induced bacterial death [10], the MIEs involved in these toxicity pathways are rarely reviewed.

In this report, we summarized the MIEs of GO in bacteria and discussed the key physicochemical properties of GO that contribute in bacterial killing efficiencies as well as MIEs. Since GO is found to induce significant toxicity in mammalian cells or animals [12], substantial concerns on the biosafety of GO have been raised. Therefore, we also discussed the biohazard effects of GO in mammals from the perspective of speeding up its clinical and commercial use in antibacterial products.

2. Structure-activity relationships (SARs) of GO in antibacterial effects

2.1. Size

GO exhibits both lateral and vertical structures, however, its lateral diameters are tens to hundreds of times larger than the vertical thicknesses [13–16]. Atomic force microscopy (AFM) and transition electron microscopy (TEM) are popularly used to characterize the primary sizes of GO [17], while the hydrodynamic sizes of GO in solutions are estimated using dynamic light scattering methods.

The layer numbers (thicknesses) of GO have been demonstrated to significantly affect its antimicrobial activities [18]. Along with the increasing of GO thicknesses from few to tens of nanomaterials, its dispersibility in biological media displays a remarkable decrease, resulting in GO agglomerate formation, which may affect the interactions between GO and bacteria [15]. Therefore, monolayer GO has been reported to exhibit higher antibacterial activities than multilayer GO [19].

The lateral sizes are also found to influence the antibacterial activities of GO by altering its adsorption abilities, dispersibilities and the number of corners and sharp edges [20]. Usually, GO with larger lateral sizes can bind bacterial cells more easily and show stronger bacterial killing [17]. When the lateral sizes of GO were reduced to several nanometers (e.g., graphene quantum dots), their antibacterial activities had a dramatic decrease due to the increases of hydrophilicity and biocompatibility [21]. However, Perreault et al. [16] found that smaller GO exhibited higher antimicrobial activity than the larger one. When the surface areas of GO nanosheets decreased from 0.65 to 0.01 μm^2, their bactericidal effects increased four folds, which could be ascribed to the excessive active defects on the surfaces of smaller GO (Fig. 2). These contradictory results imply that size may be not the only contributor for GO-induced bacterial death.

2.2. Shape

Shapes are considered to directly impact the interactions between GO nanosheets and bacterial cell membranes [22–25]. Although this assumption is difficult to be proved in experiments, recent progresses on cloud computing and machine learning have allowed theoretical simulations to predict the GO-bacteria interactions. Li et al. [26] found that GO nanosheets with sharp corners and edge protrusions can easily permeate into bacterial membrane, because this unique structure makes the penetration process undergoes a lower energy barrier [26]. Zeng's group [27] simulated the interaction between GO and cell membrane by molecular dynamics, suggesting that the unique two-dimensional (2D) structure enables robust adsorption of lipid molecules on GO surface. Interestingly, a recent study highlighted the contributions of surface curvature of GO in bacterial killing. Two types of graphene quantum dots (GQDs) derived from C_{60} and GO exhibited different bacterial killing effects (Fig. 3a and b). C_{60}-GQDs are more potent (~100% killing) against the spherical bacteria compared to