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Review

Dual-function antibacterial surfaces for biomedical applications

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ABSTRACT

Bacterial attachment and the subsequent formation of biofilm on surfaces of synthetic materials pose a serious problem in both human healthcare and industrial applications. In recent decades, considerable attention has been paid to developing antibacterial surfaces to reduce the extent of initial bacterial attachment and thereby to prevent subsequent biofilm formation. Briefly, there are three main types of antibacterial surfaces: bactericidal surfaces, bacteria-resistant surfaces, and bacteria-release surfaces. The strategy adopted to develop each type of surface has inherent advantages and disadvantages; many efforts have been focused on the development of novel antibacterial surfaces with dual functionality. In this review, we highlight the recent progress made in the development of dual-function antibacterial surfaces for biomedical applications. These surfaces are based on the combination of two strategies into one system, which can kill attached bacteria as well as resisting or releasing bacteria. Perspectives on future research directions for the design of dual-function antibacterial surfaces are also provided.

1. Introduction

Bacterial attachment and the subsequent proliferation and colonization of bacteria on the surfaces of synthetic materials usually result in the formation of a biofilm [1–4]. This bacterial biofilm poses a major problem in both human healthcare and industrial applications, including but not limited to public health settings, surgical equipment, biosensors, textiles, water purification systems, and packaging [5,6]. For medical implants and devices, bacterial attachment adversely affects the functionality and limits the lifetime of devices, and bacterial infections represent a common and substantial complication in the clinic, sometimes even leading to death [7,8]. For food processing and packaging materials, the accumulation of bacteria has a serious impact on processing efficiency, productivity, and food quality [9]. For marine equipment, microbial contamination on surfaces provides an easily accessible platform for other marine species to attach and proliferate, leading to an increase in the cost of operation and maintenance [10]. To solve these problems, considerable efforts have been directed toward developing antibacterial surfaces that can greatly reduce the extent of initial bacterial attachment and thereby prevent subsequent biofilm formation [11–16].

In recent decades, various antibacterial surfaces have been designed, which can be divided into three categories based on the their operating mechanisms: (i) bactericidal surfaces for killing attached bacteria; (ii) bacteria-resistant surfaces for preventing the initial attachment of bacteria; and (iii) bacteria-release surfaces for reducing the adhesion between bacteria and material surfaces and facilitating the release of attached bacteria by an external force. Although remarkable progress has been made in the development of these antibacterial surfaces, each methodology has inherent advantages and disadvantages. For example, bactericidal surfaces can prevent the formation of viable biofilms, but these surfaces will still be contaminated by remaining dead bacteria, which may trigger immune responses or inflammation [17]. In addition, these surfaces suffer the problems of ecotoxicity of biocides toward non-targeted species and poor compatibility with mammalian cells. On the other hand, bacteria-resistant surfaces or bacteria-release surfaces can prevent or reduce the initial attachment of bacteria; however, to date, no such surfaces can achieve 100% prevention of bacterial attachment, inevitably becoming colonized by bacteria that are not killed once they attach themselves to the surfaces. Therefore, an ideal antibacterial surface that can perform the following functions is required: (i) first, prevent initial bacterial attachment; (ii) subsequently, kill all bacteria that manage to overcome this anti-adhesion barrier; and (iii) finally, remove dead bacteria. To achieve this goal, several groups have developed surfaces by combining two strategies into one system. Over the past decade, excellent reviews on the fabrication and application of antibacterial surfaces with a single functionality have been published [18–22]; however, to the best of our knowledge, few reviews on dual-function antibacterial surfaces have been published [23].

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In this review, we first briefly introduce three main strategies for designing antibacterial surfaces with a single functionality: bactericidal surfaces, bacteria-resistant surfaces and bacteria-release surfaces. We then highlight recent developments in the creation of dual-function antibacterial surfaces based on the combination of two strategies (e.g., kill/resist or kill/release) into one system for biomedical applications. Finally, we conclude by presenting future research directions for developing dual-function antibacterial surfaces.

2. Basic strategies for designing antibacterial surfaces

2.1. Bactericidal surfaces

Bactericidal surfaces refer to surfaces that are capable of killing bacteria. According to the killing mechanism, these surfaces can be divided into two main categories: contact-based bactericidal surfaces and release-based bactericidal surfaces.

2.1.1. Contact-based bactericidal surfaces

Contact-based bactericidal surfaces are surfaces that are coated with antibacterial agents by either covalent conjugation or physical adsorption to kill adhering bacteria. The antibacterial agents used in this respect range from synthetic chemicals such as quaternary ammonium compounds (QACs), polycations and various antibiotics to natural biomolecules such as chitosan, antimicrobial peptides (AMPs) and antimicrobial enzymes (AMEs). Herein, we introduce several typical examples.

QACs with both long hydrophobic alkyl chains and positively charged quaternary ammonium groups have been demonstrated to show strong contact-killing activity toward both Gram-positive and Gram-negative bacteria. The ion exchange of QAC molecules with Ca^{2+} and Mg^{2+} ions in the cytoplasmic membrane destabilizes the intracellular matrix of a bacterium; additionally, the hydrophobic tail interdigitates into the hydrophobic bacterial membrane over the entire surface area of a bacterium, causing general perturbations in the cytoplasmic membrane and leakage of intracellular fluid containing essential molecules [24,25]. One typical QAC is the quaternary ammonium silane of 3-(trimethoxysilyl)-propyldimethyloctadecyl ammonium chloride (QAS, Fig. 1a), which can be easily immobilized onto OH-containing surfaces (such as silicone rubber [26], cotton [27], titanium [28], silica particle [29], and cellulose [30]) by covalent bonds. In addition to QAS, polymers with quaternary ammonium groups in their side chains have also been explored as polymeric biocides. Quaternized poly(4-vinyl-*N*-alkylpyridinium bromide) (PVP, Fig. 1b) [31,32] and quaternized poly(2-(dimethylamino ethyl) methacrylate) (PDMAEMA, Fig. 1c) [33–35] are two typical biocidal polymers. For more information on antibacterial polymers, readers may refer to other reviews [20,36,37].

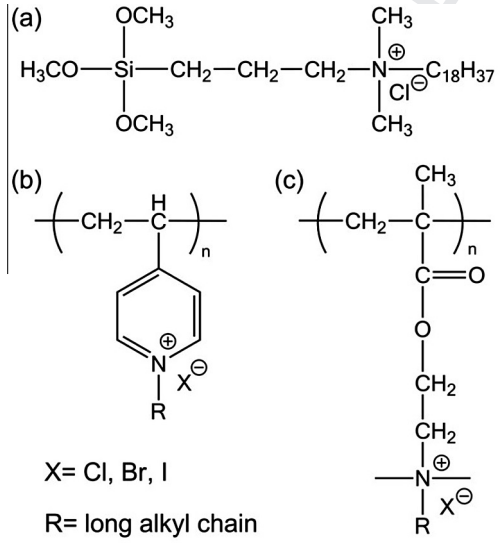

Fig. 1. Chemical structures of (a) 3-(trimethoxysilyl)-propyldimethyloctadecyl ammonium chloride (QAS), (b) quaternized poly(4-vinyl-*N*-alkylpyridinium bromide) (PVP), and (c) quaternized poly (2-(dimethylamino ethyl) methacrylate) (PDMAEMA).

AMPs and AMEs represent natural alternatives to traditional synthetic biocidal compounds for developing bactericidal coatings. AMPs form an integral part of the innate immune system in most organisms. The advantages of AMPs include limited immunogenicity, rapid bactericidal behavior, and less susceptibility to proteolysis [38]. AMEs refer to a group of enzymes with abilities to directly attack the microorganism, interfere with biofilm formation, and/or catalyze reactions which result in the production of antimicrobial compounds [39]. According to the antibacterial mechanism, they can be divided into three categories: proteolytic enzymes, polysaccharide-degrading enzymes, and oxidative enzymes [40]. AMPs and AMEs can be immobilized on supporting surfaces either physically (e.g., *via* adsorption or layer-by-layer assembly) or chemically (e.g., *via* covalent bonding) to fabricate bactericidal coatings with a broad spectrum of antibacterial activity, high efficacy even at low concentrations, and lack of susceptibility to bacterial resistance [39–41].

2.1.2. Release-based bactericidal surfaces

Release-based bactericidal surfaces are surfaces within which biocides are preloaded or embedded before being released slowly into the environment to kill bacteria. The most widely used biocides are silver nanoparticles (AgNPs) because of their strong and broad-spectrum antibacterial characteristics [8,15,42–44]. The main mechanism through which AgNPs exert their biocidal properties is through the release of Ag^{+} ions, which damage the bacterial membrane as well as disrupt the function of bacterial enzymes and/or nucleic acid groups in cellular protein and DNA [45]. There are also several types of release-based bactericidal surfaces that use antibiotics [46–48] or nitrogen oxide [49–51] as releasing biocides to avoid bacterial infection.

2.1.3. Dual-contact- and release-based bactericidal surfaces

Several bactericidal surfaces with two different biocides incorporated into one system operate through both contact-based and release-based mechanisms. These surfaces are of particular interest because they can minimize the selection and proliferation of resistant strains, providing long-term antibacterial efficiency. For example, a thin film coating composed of two distinct, layered functional regions (i.e., a polyelectrolyte multilayer reservoir for the loading and release of bactericidal AgNPs and a SiO_2 surface cap with immobilized QAS, as shown in Fig. 2) was developed [52]. Dual-function coatings of this type show high initial

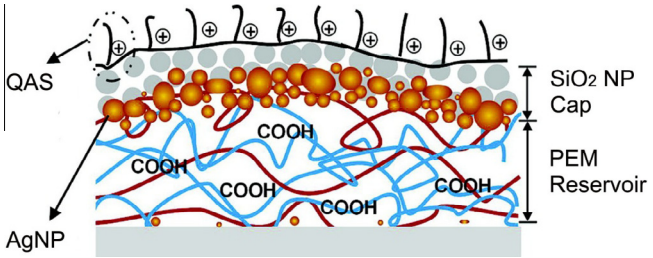

Fig. 2. Schematic illustration of a two-level dual-function bactericidal coating with both QAS and AgNPs. Reprinted with permission from Ref. [52], Copyright 2006, American Chemical Society.

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