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Review

Antibacterial Coatings: Challenges, Perspectives, and Opportunities

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Antibacterial coatings are rapidly emerging as a primary component of the global mitigation strategy of bacterial pathogens. Thanks to recent concurrent advances in materials science and biotechnology methodologies, and a growing understanding of environmental microbiology, an extensive variety of options are now available to design surfaces with antibacterial properties. However, progress towards a more widespread use in clinical settings crucially depends on addressing the key outstanding issues. We review release-based antibacterial coatings and focus on the challenges and opportunities presented by the latest generation of these materials. In particular, we highlight recent approaches aimed at controlling the release of antibacterial agents, imparting multi-functionality, and enhancing long-term stability.

Trends

Coatings releasing antibacterial agents have shown great potential to reduce nosocomial infections.

The development of controlled release strategies is necessary to optimize therapeutic effects.

Next-generation coatings should be multifunctional and integrate multiple antibacterial effects.

Standardized assessment of both stability and antibacterial properties still need to be addressed, especially for long-term applications.

Antibacterial Surfaces in Health Applications

Advances in Biomedical Engineering Prompted by the Development of New Materials

Recent advances in materials science have brought about high-performance, multifunctional materials with bioactive properties [1]. Materials bulk properties determine the general mechanical behavior, while bioactivity is linked to surface properties. The main driving force for developing biocompatible coatings is the increased performance of functionalized surfaces that cannot be achieved by bulk materials. Thin films can simultaneously satisfy multiple requirements with respect to stability in biological environments, for example, mechanical (hardness, Young's modulus, stress), tribological (wear resistance, friction, adhesion), chemical (corrosion resistance), and others.

Nosocomial Infections and the Role of Surfaces

So-called nosocomial (hospital-acquired) infections result from hospital or healthcare service unit treatment, but are secondary to the original condition of the patient [2]. Such infections are considered a major health challenge in healthcare units worldwide. The prevalence rate of nosocomial infections, which are primarily caused by bacterial colonization of a broad range of biomedical surfaces, generally ranges from 4% to 10% (reaching up to 30% in intensive care units) in western-industrialized countries, making them the sixth leading cause of death [3–6]. The proportion is typically higher (>15%) in the developing world [7]. It is fortunate that the operating room is a sterile environment because it is filled with the largest number of potentially-infectious objects: instruments, the back table, the surgical table, monitoring/anesthesia equipment, and drapes. Although ventilation follows strict requirements during the design of an operating room, it is also considered as a major cause of bacterial contamination at the surgical area [8]. Consequences are catastrophic, especially in high-risk operations (open heart, prosthesis implantation, etc.). In

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2011, an estimated 722 000 nosocomial infections occurred in the USA, resulting in nearly 75 000 deaths [9]. Estimates of the annual cost range from $4.5 billion to over $11 billion.

It is now widely accepted that bacteria survive by attaching to solid substrates, in sessile structured communities called biofilms, where they can persist for extended periods, acting as a reservoir of pathogens and multiplying their pathways of transmission [10,11]. Bacteria in biofilms are drastically more resistant to antibiotics and external forces and can withstand host immune responses [12]. In addition, most nosocomial infections can be attributed to Gram-negative bacterial pathogens, for which there is a dwindling supply of antibiotics [13]. There is also increasing epidemiological evidence that, in addition to indwelling devices and implants, surfaces in the near-patient environment play a major role in the spread of nosocomial infections [9,14,15].

Importance of Antibacterial Coatings

Preventing the bacterial colonization of biomedical surfaces is the key to limiting the spread of infections. Nowadays, the bulk properties (e.g., mechanical) of materials in health applications have been more or less fully optimized. On the other hand, thin films can impart desired surface functions without affecting bulk mechanical properties. Antibacterial coatings have become a very active field of research, strongly stimulated by the increasing urgency of identifying alternatives to the traditional administration of antibiotics.

There are three major strategies for designing antibacterial coatings: antibacterial agent release, contact-killing, and anti-adhesion/bacteria-repelling (Box 1). The last two non-release approaches will be only briefly described in this review; interested readers are directed to other

Box 1. Main Approaches to Antibacterial Surfaces

Antibacterial Agent Release

Release-based coatings exert their antibacterial activity by leaching loaded antibacterial compounds over time, which allows killing of both adhered and adjacent planktonic bacteria. The release of incorporated antibacterial agents is achieved by diffusion into the aqueous medium, erosion/degradation, or hydrolysis of covalent bonds [31]. Compared with traditional antibiotic delivery methods, direct elution from the material surface offers the possibility to deliver a high antibacterial agent concentration locally, without exceeding systemic toxicity or ecotoxicity limits. It provides antibacterial activity only where needed, thus minimizing the development of resistance and avoiding potentially harmful systemic repercussions. However, because coatings have inherently limited reservoirs of antibacterial agents, their action is ultimately only temporary.

Contact-Killing

Contact-killing coatings have been developed to circumvent the reservoir exhaustion issue of release-based materials [115]. In this approach, antimicrobial compounds are covalently anchored to the material surface by flexible, hydrophobic polymeric chains. Adhered bacteria are believed to be killed due to disruption of their cell membrane by the attached compounds, reaching across the microbial envelope thanks to the long tethering chains [26]. Because the main mechanisms of action are based on membrane interactions, such as physical lysing or charge disruption, the most effective compounds for contact-killing coatings have been either cationic compounds (QACs, chitosan, AMPs, etc.) or enzymes [17].

Anti-Adhesion/Bacteria-Repelling

Anti-adhesion coatings seek to prevent the earliest step of biofilm formation using non-cytotoxic mechanisms. Bacterial adhesion at biomaterial surfaces is generally described using a two-stage model: an initial, rapid and reversible stage (stage I), mediated by non-specific physicochemical interactions, followed by a secondary 'locking' stage (stage II) involving, among others, species-specific bacterial adhesion proteins [116]. Surface immobilization of molecules that can resist protein adsorption, such as PEG and zwitterion, have demonstrated great anti-adhesion properties *in vitro* and, despite stability issues, are generally regarded as the standard approach for anti-adhesion coatings. However, the use of physical surface modifications (especially surface topography) as non-specific methods to modulate bacterial adhesion is most likely more complex than previously thought [103,117,118].