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Review article

Polysaccharide-based antibiofilm surfaces

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ABSTRACT

Surface treatment by natural or modified polysaccharide polymers is a promising means to fight against implant-associated biofilm infections. The present review focuses on polysaccharide-based coatings that have been proposed over the last ten years to impede biofilm formation on material surfaces exposed to bacterial contamination. Anti-adhesive and bactericidal coatings are considered. Besides classical hydrophilic coatings based on hyaluronic acid and heparin, the promising anti-adhesive properties of the algal polysaccharide ulvan are underlined. Surface functionalization by antimicrobial chitosan and derivatives is extensively surveyed, in particular chitosan association with other polysaccharides in layer-by-layer assemblies to form both anti-adhesive and bactericidal coatings.

Statement of Significance

Bacterial contamination of surfaces, leading to biofilm formation, is a major problem in fields as diverse as medicine, first, but also food and cosmetics. Many prophylactic strategies have emerged to try to eliminate or reduce bacterial adhesion and biofilm formation on surfaces of materials exposed to bacterial contamination, in particular implant materials.
Polysaccharides are widely distributed in nature. A number of these natural polymers display antibiofilm properties. Hence, surface treatment by natural or modified polysaccharides is a promising means to fight against implant-associated biofilm infections. The present manuscript is an in-depth look at polysaccharide-based antibiofilm surfaces that have been proposed over the last ten years. This review, which is a novelty compared to published literature, will bring well documented and updated information to readers of Acta Biomaterialia.

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1. Introduction

It is now well recognized that bacteria attach to solid supports to form structured communities called biofilms, defined as biopolymer matrix-enclosed microbial populations adhering to each other and/or surfaces [1]. Biofilms occur on both inert and living supports in all environments [2]. They affect many industrial and domestic domains [3] and are responsible for a wide range of human infections [1]. Considering the ever increasing number of implanted patients, biofilm-associated infections of indwelling medical devices are more particularly a major public health concern. Examples of implants that can be affected by biofilm formation are catheters (intravascular, urinary), mechanical heart valves, vascular prostheses, pacemakers/defibrillators, ventricular assist devices, coronary stents, neurosurgical ventricular shunts, cerebrospinal fluid shunts, neurological stimulation implants, joint prostheses (hip, knee, ...), fracture-fixation devices, breast, inflatable penile, cochlear and dental implants, ocular prostheses and contact lenses, intrauterine contraceptive devices [4–6]. Bacteria commonly isolated from biofilm-infected implants include the gram-positive *Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermidis* and *Streptococcus mutans*, and the gram-negative *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* and *Pseudomonas aeruginosa* ([7]; see also [8] for a more detailed list including fungi and yeasts). Biofilm-associated infections are particularly problematic because sessile bacteria are much more resistant to antibiotics and biocides than their planktonic counterparts [9]. Hence, the treatment of biofilm infections needs high concentrations of disinfectants or antibiotics, which may cause severe environmental damages and multiresistance emergence. In this context, prevention of biofilm formation is actually preferable to any post-infection treatment.

At the biomaterial surface level, two main strategies are currently proposed to oppose biofilm formation, i.e., the development of anti-adhesive or bactericidal surfaces (Fig. 1) – the use of biofilm-degrading agents [11] being still in its infancy. Surfaces that are mainly repellent are characterized by a decrease in the number but no significant loss in viability of attached bacteria. Anti-adhesive properties of inert materials can be improved by modifying surface characteristics known to affect microbial cell adhesion, namely surface topography (roughness) and physicochemistry (surface free energy, hydrophilic or hydrophobic, cationic or anionic behavior) [12–15]. A physical treatment of the surface such as plasma irradiation followed or not by attachment of anti-adhesive molecules or polymers, is commonly applied for that purpose [16]. However, sustained cell adhesion on implanted materials is required for suitable tissue integration of permanent implants such as vascular grafts or joint prostheses. Hence, the properties of such implant surfaces must balance between repellency against bacterial cells and adhesiveness for tissue cells, controlling the "race for the surface" [17,18] between bacteria and tissue cells. Killing effect of the surface against attached and/or suspended bacteria is highlighted by a decrease in adherent cell viability and/or the number of viable suspended cells. As shown in Fig. 1, bacterial killing properties can be achieved by non-covalent immobilization of an antimicrobial agent through direct incorporation in the biomaterial bulk or deposition on the surface (previously modified or not), leading to progressive release of the drug in the surrounding medium. Another way consists in covalent binding (i.e., with no leakage) of an antibacterial compound to the biomaterial surface to yield a contact-killing coating. The first method has been widely used in commercial devices such as catheters that are heparinized for thromboresistance and loaded with antimicrobials (e.g., Ag^+ ions, chlorhexidine, benzalkonium chloride, minocycline-rifampicin) [19]. The covalent method presents the advantage of avoiding potential toxic effects of classical biocidal compounds and loss in efficiency due to a limited reservoir capacity of the biomaterial [20]. Moreover, both strategies could be mixed to elaborate infection-resistant biomedical materials with synergic anti-adhesive and bactericidal properties.

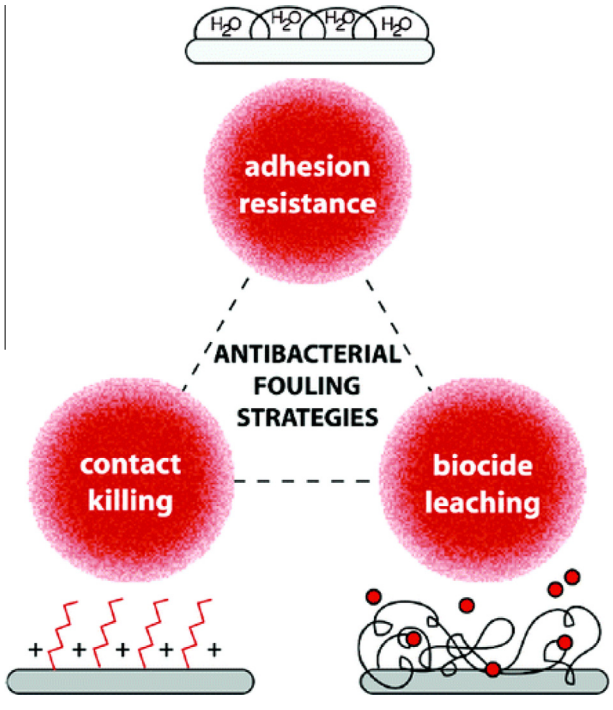

Fig. 1. Main strategies for antibacterial surface design. Taken from [10].

One of main features of biofilm formation is the production of an extracellular matrix composed of 90% water and 10% extracellular polymeric substances [21]. The latter are mainly composed of polysaccharides and proteins, but also include nucleic acids, lipids and other biological macromolecules. Their components mediate cell-to-cell and cell-to-surface interactions that are necessary for biofilm formation and stabilization [21]. Some observations also suggest that some bacterial extracellular polysaccharides might inhibit and/or destabilize the biofilm (see [22,23] and references therein). However, none of antibiofilm exopolysaccharides identified so far exhibits antibacterial activity. Most of them act as surfactant molecules, modifying the physical characteristics of bacterial cells and abiotic surfaces [23]. On the other hand, several bacterial exopolysaccharides have been shown to display antimicrobial efficiency [24–27], as have been chitosan, a chitin derivative [28], and a number of polysaccharides of algal [29,30], fungal [26,31] and plant [32,33] origins.

Hence, modified polysaccharides are being developed as bacteria-repellent and/or -killing coatings for material surfaces exposed to biofilm formation. The following is an in-depth look at polysaccharide-based antibiofilm surfaces that have been proposed over the last ten years, focusing in particular on bactericidal coatings that mainly involve chitosan and its derivatives.

2. Anti-adhesive surfaces

Prevention of bacterial adhesion on surfaces through anti-adhesive coatings is one of the simplest, potentially cost-effective ways to avoid biofilm formation. Bacterial adhesion is a complex process which is affected by many factors including – as stated above – the physical and chemical characteristics of material surface, but also bacterial cell properties (e.g., hydrophobicity