Chapter 5
Antimicrobial/Antifouling Surfaces Obtained by Surface Modification

Abstract A major issue in the use of biomaterials in natural environments and in particular in hospitals is related to the microorganism adhesion to the biomaterial surface. In this context, the focus of scientists and biomedical manufacturers turned to the development of coatings capable of resisting bacterial colonization and that can be placed on the surfaces of medical devices.

In this chapter, a variety of concepts and approaches are currently being explored in order to produce materials with anti-infective properties that could be employed for biorelated applications will be described. As will be depicted, the strategies are proposed to either reduce or prevent bacterial adhesion. They basically can be divided into two different methodologies: the first type of methodologies include those strategies that either involve chemical modification to introduce antimicrobial activity or are intrinsically antimicrobial. The second type refers to those methodologies that resort to the formation of micro/nanostructures at the biomaterial surface. This chapter will focus on the first group, i.e., the description of the different strategies to chemically modify the polymer surface to improve their antifouling properties or to provide antimicrobial activity.

However, prior to the description of the different methodologies to fabricate antimicrobial surfaces the approaches that are available in order to modify the chemical composition of a particular surface will be first analyzed.

Keywords Surface modification • Antimicrobial surface • Grafting from • Grafting onto • Biocide-releasing coatings • Bioactive materials

5.1 Introduction

A major issue in the use of biomaterials in natural environments and in particular in hospitals is related to the microorganism adhesion to the biomaterial surface. In this context, the focus of scientists and biomedical manufacturers turned to the

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development of coatings capable of resisting bacterial colonization and that can be placed on the surfaces of medical devices [1, 2].

Microorganisms and in particular bacteria adhere to almost all kind of surfaces. Upon adhesion they are able to grow and produce a matrix containing extracellular polymeric substances that may, in a further step, form a biofilm. As a result, patients might suffer from acquired infections like ventilator-associated pneumonia, catheter-associated urinary tract infection, and central line-associated blood stream infections. For instance, the annual infection rate for cardiovascular implants is even higher (7.4 %) [3]. In addition, a particular concern is that once the biofilm is formed antibiotics administered systemically are not effective against implant-associated infections. As a result, the strategy followed resort to implant removal and/or amputation.

In this context, a large variety of concepts and approaches are currently being explored in order to produce materials with anti-infective properties that could be employed for biorelated applications [4]. In Fig. 5.1 are depicted the different strategies proposed to either reduce or prevent bacterial adhesion. They basically can be

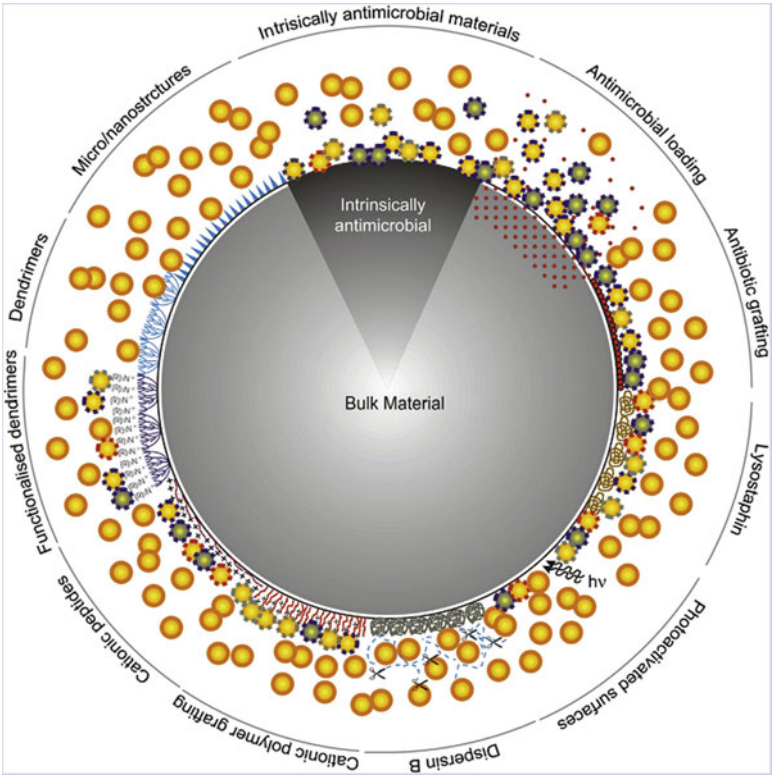


Fig. 5.1 Overview of the strategies to modify biomaterial surfaces to prevent biomaterial-associated infections. Reproduced with permission from [4]

divided into two different methodologies: the first type of methodologies include those strategies that either involve chemical modification to introduce antimicrobial activity or are intrinsically antimicrobial. The second type refers to those methodologies that resort to the formation of micro/nanostructures at the biomaterial surface. This chapter will focus on the first group, i.e., the description of the different strategies to chemically modify the polymer surface to improve their antifouling properties or to provide antimicrobial activity. Those approaches to produce antimicrobial surfaces based on their structuration will be considered in Chap. 6.

However, prior to the description of the different methodologies to fabricate antimicrobial surfaces the approaches that are available in order to modify the chemical composition of a particular surface will be first analyzed.

5.2 Polymer Surface Modification

As has been mentioned above, once the biofilms have been developed on the material surface they are extremely hard if not impossible to remove and show great resistance to a great variety of biocides. As a result, the most extended strategy to prevent infection and material deterioration is to prevent the biofilm formation. In this context, the primary adhesion of microbial cells must be avoided. As depicted in Fig. 5.2, this objective has been mainly pursued by modifying the polymeric interface using two different strategies, i.e., using repelling or killing molecules. Repelling coatings resort, for instance, to the immobilization of polyethylene glycol (PEG) segments at the surface, by anchoring highly negatively charged polymers that repel the bacterial adhesion based on electrostatic repulsion or modifying the surface with ultrahydrophobic moieties.

Alternatively, microbes adhering to the surfaces can be killed by releasing a biocide. The biocide can be either embedded in the polymer matrix or generated

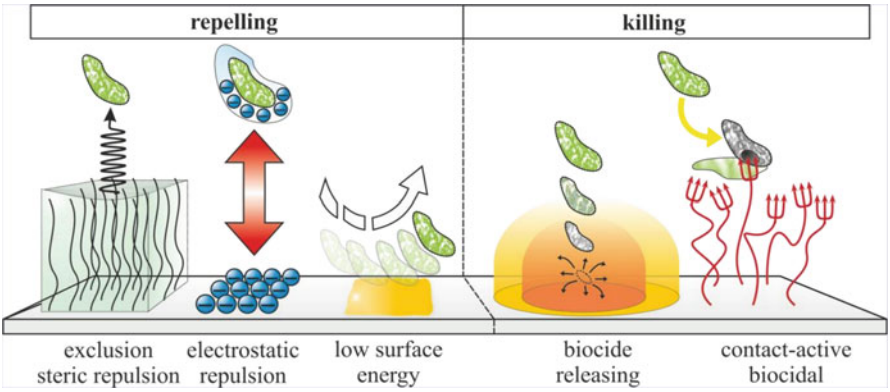


Fig. 5.2 Alternative approaches to prepare either antifouling or antimicrobial surfaces. Reproduced with permission from [5]

in situ, by formation of active species. For instance, reactive oxygen species (ROS) can attack a diverse range of targets to exert antimicrobial activity. These species are versatile in mediating host defense against a broad range of pathogens [6]. Alternatively to these strategies, surfaces can also be rendered contact-active antimicrobial upon tethering antimicrobial polymers. In this chapter, we will limit our discussion to the surface modification with antifouling and antimicrobial polymers [5].

Whereas pioneer advances on the development of materials and surfaces with antibacterial properties were based on empirical analysis, today significant advances on the causes of infection allowed us to explore different strategies to prevent bacterial adhesion. In particular, this chapter will summarize the strategies explored to modify surfaces of commonly used polymers. In order to fabricate materials with infection-resistant properties, the surface chemical composition can be varied using different alternatives including material surfaces with antimicrobials, surfactants, repellent coatings, or with selected biological molecules, such as heparin or albumin [7–12].

However, as reported by Siedenbiedel and Tiller [5] the strategies to chemically modify polymer surfaces in order to avoid bacterial adhesion and, therefore, biofilm formation can be grouped into two main alternatives (Fig. 5.2) [5, 13–19]. On the one hand, surfaces can be modified introducing repelling groups that act using different forces such as electrostatic repulsion, low surface energy, or exclusion steric repulsion. On the other hand, modified surfaces can be prepared by immobilization/release of antimicrobial compounds capable of killing bacteria upon contact with the material surface.

5.3 Techniques to Functionalize Polymer Surfaces

The strategies to functionalize polymer surfaces reported can be grouped in three main alternatives (Fig. 5.3). The first strategy involves the physical immobilization of polymer chains, i.e., by non-covalent attachment. Within this approach, layer-by-layer deposition [21] or dip coating [22] processes have been employed to prepare antimicrobial coatings. Although this strategy is very simple and can be carried out without the use of sophisticated chemical approaches, there are few limitations on their use. On the one hand, the mechanical stability of these interfaces is reduced and changes in the environmental conditions (temperature, pH, …) can produce significant changes. On the other hand, biocide leaching may lead to a rapid loss of the antimicrobial activity [23].

As an alternative to this approach, covalent immobilization of the antimicrobial moieties can be achieved by using either grafting-to or grafting-from methodologies. Grafting-to resorts to the immobilization of preformed chains to a polymer surface by a coupling reaction. This approach permits the formation of a homogeneous layer of antimicrobial polymers in which the chemical properties such as monomer composition or chain length can be easily controlled. Moreover, the

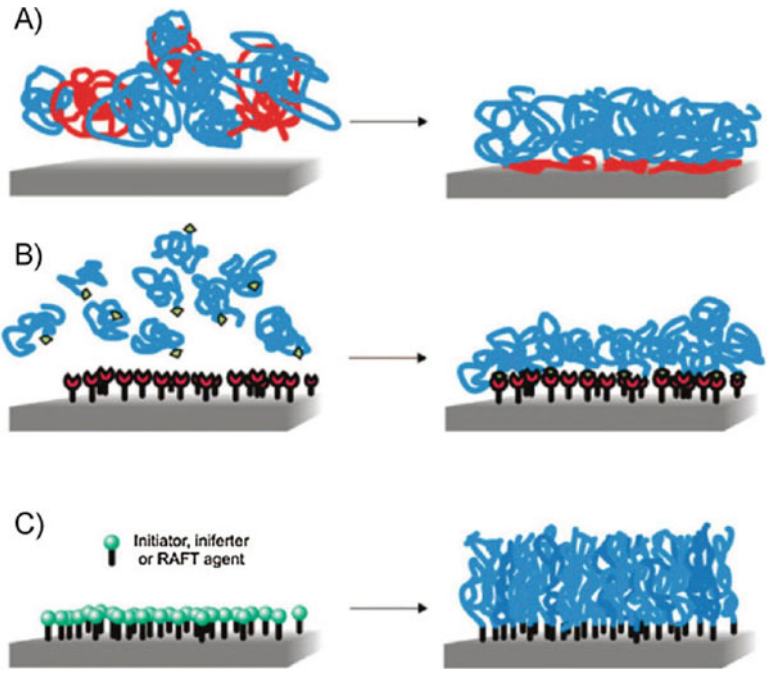


Fig. 5.3 Strategies to immobilize polymer chains (**a**) Physical adsorption by non-covalent interactions. Dominated by the preferential adsorption of the *red* blocks to the surface, e.g., LbL films, block copolymer coatings, (**b**) Grafting-to methods by creating covalent bonds with complementary groups at the surface, e.g., PEIs (poly(ethylene imine)), cationic polymers, (**c**) Grafting-from or surface-initiated polymerization via synthesis of antimicrobial coating from initiators revealed at the surface by ATRP, e.g., PVP, PDMAEMA, methacrylates. Reproduced with permission from [20]

covalent bonds established between the polymer and the surface does not allow the biocide to leach thus enabling a long-term use of the material.

Similarly to the grafting-onto, grafting-from enables produces covalently anchored functional surfaces. In this case, an initiator present at the surface can be employed to polymerize. Controlled radical polymerization such as atom transfer radical polymerization (ATRP) or reversible addition fragmentation chain transfer polymerization (RAFT) produced coatings with polymer chain having narrow polydispersity. A major advantage in comparison with the grafting-to approach, concerns the higher chain density that can be achieved using this strategy.

It is worth mentioning that most of these elaborate techniques are useful for preparations in the laboratory but not in the industry, because the required chemical finishing is often too expensive [5]. In Table 5.1 are summarized the different alternatives to obtain contact-active antimicrobial surfaces as well as the polymers employed and several illustrative examples.

Table 5.1 Examples of surface-attached biocidal polymers

	Method	Polymer	Examples
Grafting from	Immobilized initiator	QPAM	[16]
		PEtOx	[24]
Grafting to	Immobilized comonomer	QP4PVP	[25]
	End-on	AMP	[26, 27]
	Side-on	QPEI	[28]
		NB	[28]
	Parallel grafting to and modification	QP4PVP	[29]
	In situ end-on	PMOx	[30]
	In situ side-on	QPU	[31]
Coating	Layer by layer	Polylysine	[21]
		PAA	[32]
		PHGH	[33]
		Chitosan	[34]
	Particles with grafted polymer	Magnetic Fe_3O_4 with QPEI	[35]
		PA-particles with QP4PVP	[36]
	Hyperbranched polymers	QPEI	[22, 37]
	Plasma polymerization	PDAA	[38]
		Polyterpenol	[39]
	Surface-induced hydrogelation	Vancomycin	[40]
		AMP	[41]

Reproduced with permission from [5]
QP4VP quaternized poly(4-vinylpyridine), *QPAM* quaternized poly(*N*,*N*-dimethylaminoethylacrylamide), *PAA* poly(allylammonium chloride), *QPEI* quaternized polyethyleneimine, *PS* poly(styrene), *PEtOx* poly(2-ethyloxazoline), *PMOx* poly(2-methyloxazoline), *QPU* quaternized polyurethanes, *PN* norbonene-based polymers, *AMP* antimicrobial peptides, *PA* poly(acrylate), *PHGH* poly(hexamethylene guanidinium hydrochloride)

5.4 Anti-Adhesive Polymer Surfaces: Antifouling

Chemical modification of polymer surfaces has been demonstrated to be crucial in order to avoid bacterial contamination. For this purpose, highly hydrophobic and hydrophilic groups have been anchored on polymer surfaces. Table 5.2 includes few illustrative examples in which modified polymer surfaces have shown low bacterial adhesion properties [4].

Hydrophilic synthetic polymers can repel or reduce the microorganisms adhesion by steric hindrance [9, 53–57]. In this category also referred as "passive approach" or "bacteria-resistive" [58] we can include the formation of coatings of highly hydrated polymer chains, such as poly(ethylene glycol) (PEG) on a surface exhibits a large exclusion volume effect, which inhibits both protein and bacterial

Table 5.2 Examples of anti-adhesive coatings

Polymer coating	Monomer charge	In vitro-tested efficacy		Refs
		Gram-negative	Gram-positive	
Fluorosiloxane coatings	Superhydrophobic		SA	[42]
Poly(ethylene oxide) (PEO)	Hydrophilic, no charge	EC, PA	SA, SE, SS	[43, 44]
Poly(epsilon-caprolactone) (PCL)/PEG copolymer	Hydrophilic, no charge	BS		[45]
Phosphorylcholine (PC)-based polymers	Zwitterionic	EC, PA	SA, SM	[46, 47]
2-Methacryloyloxyethyl phosphorylcholine (MPC) polymer	Zwitterionic	PA	SA, SE	[48]
Zwitterionic poly(sulfobetaine methacrylate) (pSBMA)	Zwitterionic	PA	SE	[49–51]
Peptide-functionalized poly(L-lysine)-grafted-poly(ethylene glycol) (PLL-g-PEG/PEG-RGD)	Positively charged		SA	[52]

Adapted from [4]
EC *Escherichia coli*, PA *Pseudomonas aeruginosa*, SA *Staphylococcus aureus*, SE *Staphylococcus epidermidis*, SM *Streptococcus mutans*, SS *Streptococcus salivarius*

adhesion [59]. Equally, coatings based on heparin (highly hydrophilic polymer) also prevented the adhesion of bacterial cells [9, 10, 12].

Other alternative involves the functionalization of the surface with zwitterionic polymers and derivatives that have been employed for their antifouling properties. Zwitterionic polymers have an equivalent number of homogeneously distributed anionic and cationic groups on their polymer chains [60]. In contrast to the use of PEG, zwitterionic polymers have a broader chemical diversity and greater freedom for molecular design.

As reported by Mi and Jiang [60] important aspects related to the chemical diversity mentioned above include:

(a) Types of ionic groups (anionic and cationic) to be incorporated into the polymer structure. On the one hand, anionic groups include carboxylates [61], sulfonates [62, 63], or phosphates [64]. On the other hand, quaternary ammonium [63, 65], phosphonium [66], pyridinium [67], or imidazolium [68] have been typically employed as cationic groups.
(b) Distribution and arrangement of the charged groups. In this context, two main aspects can be varied. First, the proximity between positive and negative charges within the same monomeric unit [69]. Secondly, the total separation of oppositely charged ionic groups onto different polymer side chains (the latter case is also known as "mixed charge" polymers); [70]
(c) More sophisticated designs include the modification of typically employed zwitterionic polymers to form new polymers able to switch between zwitterionic

and non-zwitterionic forms [71–74]. Equally, these modified systems could be designed to carry a charged biologically active molecule as a part of the zwitterionic constituent [75].

It is important to mention that even if zwitterionic polymers have been mainly employed as antifouling molecules, the possibility of adjusting functional aspects, such as the ionic nature of zwitterionic materials, polymer charge density, pH sensitivity, or counterion association, have open new paths for their use as antimicrobial compounds [60].

5.5 Antibacterial Coatings

In contrast to the "passive" strategies to develop antifouling surfaces, the so-called active approaches also known as "bacteria killing" have been focused on the anchoring of molecules able to kill bacteria upon contact.

5.5.1 Biocide-Releasing Antibacterial Coatings

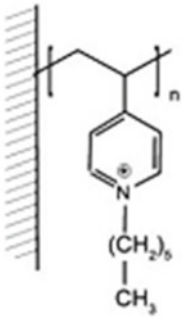
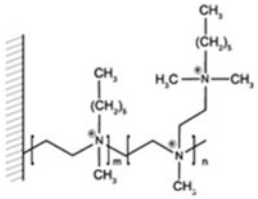
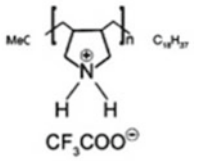
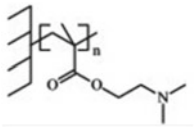
Most of the systems explored involve the incorporation of antimicrobial agents that can be gradually released into the solution for a large periods of time and simultaneously kill the bacteria present in the media [76–78].

Within this category many different antimicrobial agents have been explored with more or less success. These include quaternary ammonium compounds, iodine, silver ions, nitric oxide, or even antibiotics [4, 79]. As an example of microbicidal coating, Klibanov et al. [80] prepared both inorganic glass and polyethylene interfaces modified with of *N*-hexyl, *N*-methyl-PEI (polyethylene imine) [35, 81–83]. This strategy involves the non-covalent interactions between the PEI and the substrates. In this system, polycations leached from the surface act as antimicrobials against *S. aureus* [22]. More interestingly, replacing the short hexyl chains by longer docecyl chains resulted in a material with improved the integrity while retaining their antimicrobial activity for longer periods of time [84, 85]. However, as has been mentioned above, in some cases specially structured robust coatings and effective in resisting biofilm formation are required.

5.5.2 Intrinsically Bioactive Materials: Contact-Active Biocidals

The most extended class of polymers employed as antimicrobials are cationic polymers that are effectively adsorbed at the bacterial cell surface directed by the net negative charge of microbial cells. As depicted in Table 5.3, many different

Table 5.3 Antimicrobial coatings obtained by surface modification with cationic polymers

Name and typical structure of cationic polymeric coatings	Surface	Grafting strategy	Reference
P4VP polymeric coating 	Glass plastic	Covalent modification	[58, 61]
		Covalent modification	
PEI-based polymeric coating 	Glass textile	Covalent modification	[19, 26, 59]
		Dip coating	
Polymers with incorporated quaternary ammonium ODDMACPDDMAC 	Cellulose glass	Covalent modification	[31, 165]
		Dip coating	
PDMAIMA 	Glass inorganic surfaces plastic (polypropylene)	ATRP (grafting from) RAFT (grafting from) ATRP + covalent (grafting onto)	[70, 71, 74]

Reproduced with permission from [23]

examples have been reported in the literature of surface modification with cationic polymers involving covalent and non-covalent interactions [23]. One of pioneer works was reported by Klibanov et al. [25] that covalently linked poly(4-vinyl-*N*-alkylpyridinium bromide) to amino-modified glass slides via acylation with acryloyl chloride followed by copolymerization with 4-vinylpyridine, and finally *N*-alkylation with different alkyl bromides.

In addition to cationic polymers, another highly effective functional group in killing bacteria is based on cyclic *N*-halamine polymeric compounds [86]. In *N*-halamine, one or more halogen atoms are covalently bond to nitrogen atoms in a cyclic structure. According to current models, *N*-halamines exhibit antimicrobial properties as a consequence of the direct transfer of active halogen from the halamine groups to the cell wall of the microorganisms by direct contact followed by oxidation or by dissociation into water followed by diffusion over the microorganisms. The released halogen groups interact with the bacterial receptor thus inactivating the cell. In comparison with cationic polymers, *N*-halamines act faster but require to be regenerated. The latter occurs by exposure to dilute halogen solutions. *N*-halamines, are in addition inexpensive, nontoxic, and noncorrosive.

An illustrative example of the potential of using *N*-halamines was reported by Sun et al. [87] that described the surface modification of a polyurethane using an *N*-halamine precursor (5,5-dimethylhydantoin (DMH)). According to the authors, the *N*-halamine-based PU potent antimicrobial effects against a large variety of microorganisms: *Staphylococcus aureus* (Gram-positive bacterium), *Escherichia coli* (Gram-negative bacterium), *methicillin-resistant Staphylococcus aureus* (MRSA, drug-resistant Gram-positive bacterium), *vancomycin-resistant Enterococcus faecium* (VRE, drug-resistant Gram-positive bacterium), and *Candida albicans* (fungus). Moreover, these modifications are stable and prevented both bacterial and fungal biofilm formation during months. More interestingly, when the antimicrobial efficiency is lost due to their extensive use, it could be regenerated again by chlorination treatment as depicted in Fig. 5.4.

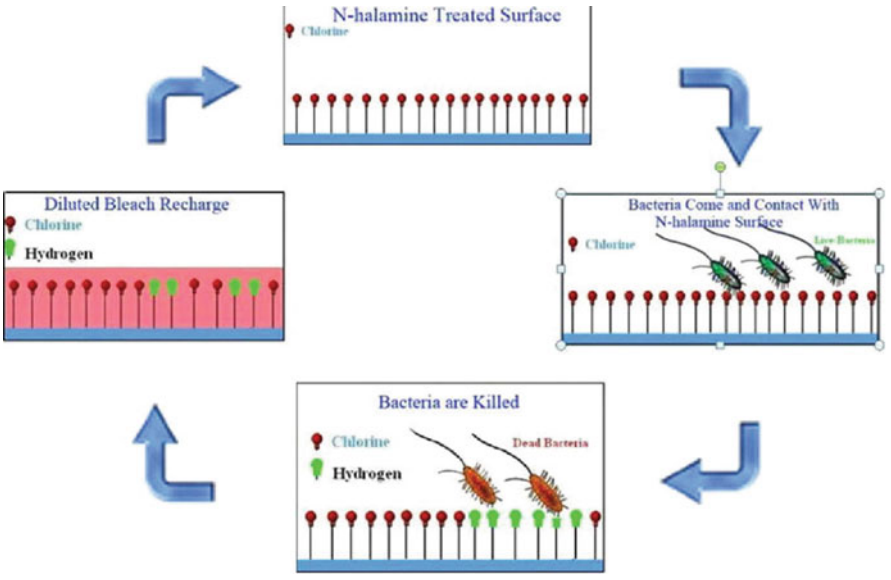


Fig. 5.4 *N*-halamine-based polyurethane surfaces are able to kill both bacteria and prevent biofilm formation. Moreover, their antimicrobial activity can be regenerated after treatment with dilute bleaching solutions. Reproduced with permission from [87]

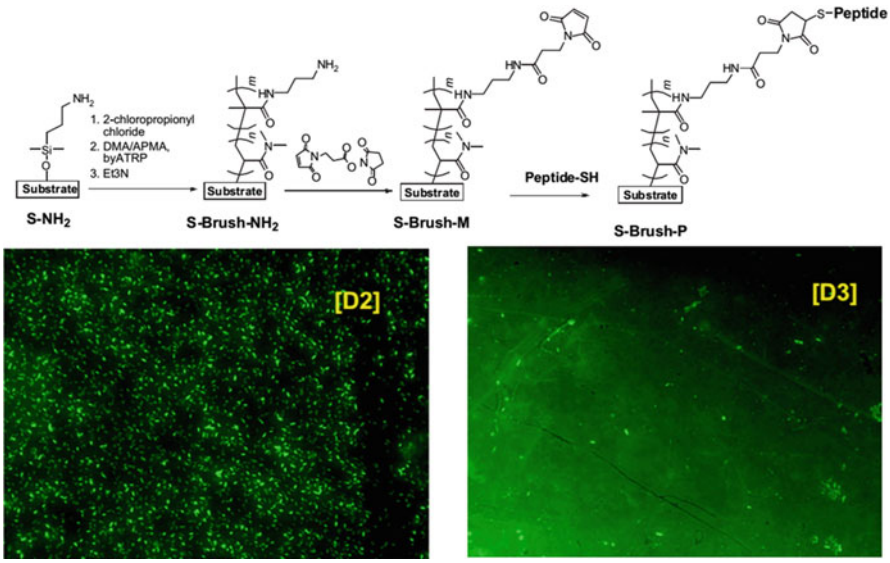


Fig. 5.5 *Above*: synthetic route for copolymer brushes and peptide conjugation. The strategy involves four steps: (*1*) surface functionalization with an initiator, (*2*) surface-initiated ATRP of *N*,*N*-dimethylacrylamide and *N*-(3-aminopropyl) methacrylamide hydrochloride, (*3*) synthesis of maleimide group immobilized Ti surface, and finally (*4*) coupling with the appropriate peptide. *Below*: (**D2**) Fluorescence image of bacteria on titanium surface, (**D3**) Fluorescence image of bacteria on peptide (Tet-26) immobilized copolymer brush on titanium surface. Reproduced with permission from [89]

Antibacterial coatings prepared by covalent immobilization of antimicrobials have been equally reported using antimicrobial peptides (AMPs). For instance, Bagheri et al. [88] reported examples of different biomaterials employed as surface supports (such as gold surfaces, resin beads, cellulose membranes, polymer brushes, and block copolymers) employed to covalently anchor cationic antimicrobial peptides. AMPs were also employed by Gao et al. [89] to modify titanium surfaces. As depicted in Fig. 5.5, this group prepared infection-resistant coatings on implants based on covalently grafted hydrophilic polymer brushes conjugated with an optimized series of tethered antimicrobial peptides. These immobilized AMPs showed broad spectrum activity against different pathogenic bacteria and yeast when immobilized on a surface.

While it is true that most of the strategies employed are directed either to prevent bacterial infections by reducing the adhesion of bacteria to the surface or to kill them when in contact with the surface recent progresses in the understanding on the molecular mechanisms of the biofilm have open the path to new alternatives to reduce the biofilm formation [4, 90, 91]. As depicted in Table 5.4, recent investigations evidenced that a large variety of substances possesses antibiofilm activities. These substances can be introduced in the grafted or can be released from the biomaterial surface [115]. Campoccia et al. [4] recently reviewed the different

Table 5.4 Examples of molecules immobilized on polymer surfaces to prevent biofilm formation

Antibiofilm molecule	Action mechanism	Ref
Hamamelitannin	Reduced biofilm metabolic activity	[92, 93]
Proteinase K	Degradation of the extracellular proteic substances of bacterial biofilms	[91]
D-aminoacids (e.g., D-leucine, D-methionine, D-tyrosine, and D-tryptophan)	They trigger biofilm disassembly and may represent a widespread bacterial signal for biofilm disassembly	[94, 95]
Norspermidine	It interacts directly and specifically with exopolysaccharide causing biofilm disassembly	[96]
Trypsin	Degradation of the extracellular proteic substances of bacterial biofilms	[97]
rhDNase I	Degradation of the extracellular-DNA (eDNA) component of bacterial biofilms	[90, 98]
Dispersin B	Degradation of the exopolysaccharidic component of bacterial biofilms	[99]
Antimicrobial peptides (AMPs)	Permeabilization of the cytoplasmic membranes. Active against quiescent bacteria	[100–102]
N-acetylcysteine (NAC)	Disruption of clinically relevant and drug-resistant bacterial biofilms. NAC inhibits exopolysaccharide expression and is also bactericidal	[91, 103]
EDTA	At low concentration bacteriostatic for planktonic cells, at higher concentrations inhibiting biofilm	[104]
Hydroxypropyltrimethyl ammonium chloride chitosan, HACC	Inhibition of polysaccharide intercellular adhesin (PIA) expression through downregulation of icaAD and upregulation of icaR in SA and SE	[105]
RNA III inhibiting peptide (RIP)	Quorum sensing-targeting	[106, 107]
Furanones	Quorum sensing-targeting	[108–110]
3-oxo-C12-(2-aminophenol)	Quorum sensing-targeting	[111]
4-Nitro-pyridine-*N*-oxide (4-NPO)	Quorum sensing-targeting	[111]
Horseradish juice extract	Quorum sensing-targeting	[110]
Norspermidine and some biomimetic guanidine and biguanide compounds	Release the protein component of EPS from the bacterial cell wall	[112]
Lysozyme	Destruction of staphylococcal cell wall. Active against quiescent bacteria	[113, 114]

Reproduced with permission from [4]

action mechanisms or currently explored active substances and distinguished four main types:

(a) Bactericidal molecules capable of killing even metabolically quiescent bacterial cells within biofilms (e.g., lysostaphin, certain AMPs)
(b) Enzymes capable of selectively degrading extracellular polymeric substances of the biofilm (e.g., Dispersin B [99], rhDNase I [90, 98])

(c) Molecules downregulating the expression of biofilm extracellular polymeric substances (e.g., *N*-acetylcysteine [91, 103]) or anyway reducing biofilm metabolism (e.g., hamamelitannin [92, 93])
(d) Molecules acting with the Quorum sensing system and inducing biofilm dispersion (e.g., furanones) [106–111]

5.6 Dual-Function Antibacterial Surfaces for Biomedical Applications

The strategies depicted above involving either the fabrication of bactericidal surfaces or bacteria-resistant surfaces have supposed important steps toward effective antimicrobial surfaces. However, limited success has been achieved since most of the systems are effective during a short-medium periods of time. In order to improve the performance of antimicrobial surfaces, many efforts have been focused on the combination different functionalities [116]. In this section, we will analyze the alternatives developed that combine two strategies acting simultaneously in one system.

5.6.1 Repelling and Releasing Surfaces

This strategy involves the use of an inherent low adhesive material incorporating active molecules. An example of this strategy involves the use of poly(vinyl alcohol) (PVA), PEG-bearing copolymers or poly(acrylic acid) derivatives hydrogel coatings that exhibit reduced microbial adhesion (around two orders of magnitude lower than uncoated control). Moreover, these hydrogels are charged with antibiotics or other biocides, so that these coatings are capable of simultaneously repelling and releasing. A rather complex design but illustrative of this approach was described by Ho et al. [117] who prepared an antimicrobial coating provided by silver ion release with a contact-killing and microbe-repelling surface. As depicted in Fig. 5.6, they fabricated a coating based on a hydrophilic polymer network of poly(2-hydroxyethylacrylate) with PEI cross-linking points. Moreover, PEI are able to form complexes with the silver ions from aqueous solution and, for upon reduction silver nanoparticles. Finally, PEGylation of these co-networks resulted in materials that efficiently kill *S. aureus* cells and still repel them after exhaustion of the silver.

5.6.2 Contact-Killing and Repelling

Laloyaux et al. [118] reported the preparation of temperature-responsive polymer brushes switching from bactericidal to cell-repellent. The system reported consists of have presented a surface that consists of surface-attached antimicrobial peptide

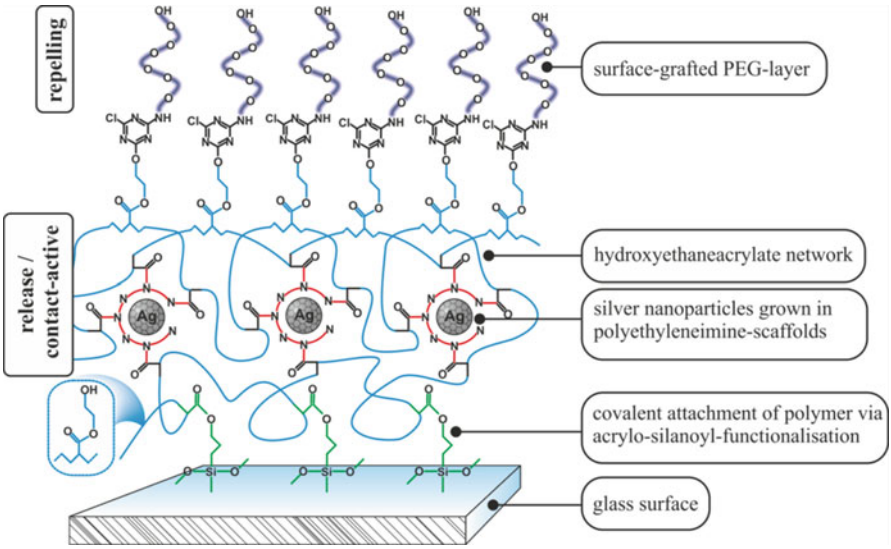


Fig. 5.6 Concept of repel and release of a designed network. Reproduced with permission from [117]

(Magainin) grafted with oligo(ethylene glycol) methacrylates (OEGMA). At room temperature, the OEGMA chains are stretched and the Magainin groups are available at the interface and effectively kill microbial cells on contact. However, upon heating above 35 °C the OEGMA collapses, the surface is mainly covered by PEG moieties at the surface. In this situation, the attached and nonattached Gram-positive bacterial cells are repelled efficiently. It is interesting to mention that, by lowering the temperature, the killing properties are reactivated. In principle, this allows to kill or repel microbial cells by reversible heating/cooling temperature cycles (see Fig. 5.7).

Another interesting examples of this strategy has been reported by Ji et al. [119]. Their approach combines heparin and chitosan embedded in a multilayer film constructed layer by layer. Chitosan (antibacterial agent) and heparin (anti-adhesive agent) were alternatively deposited onto aminolyzed poly(ethylene terephthalate) (PET) films. In their study, they correlated the hydrophobicity or hydrophilicity with the microbial adhesion. Chitosan, a pH-responsive natural polymer, exhibits significant structural changes by changing the environmental pH. Thus, at higher pH values the chitosan chains adopted loopier-type structures and tend to be adsorbed as thicker layers. On the contrary, a decrease in the pH values resulted in a reduced adsorption of chitosan to the surface. The amount of adsorbed chitosan and the hydrophilicity had a direct relation with the anti-adhesive properties of the film. The films assembled at lower pH are more hydrophilic, and this more hydrophilic surface prevented the adhesion of *E. coli* (Fig. 5.8).

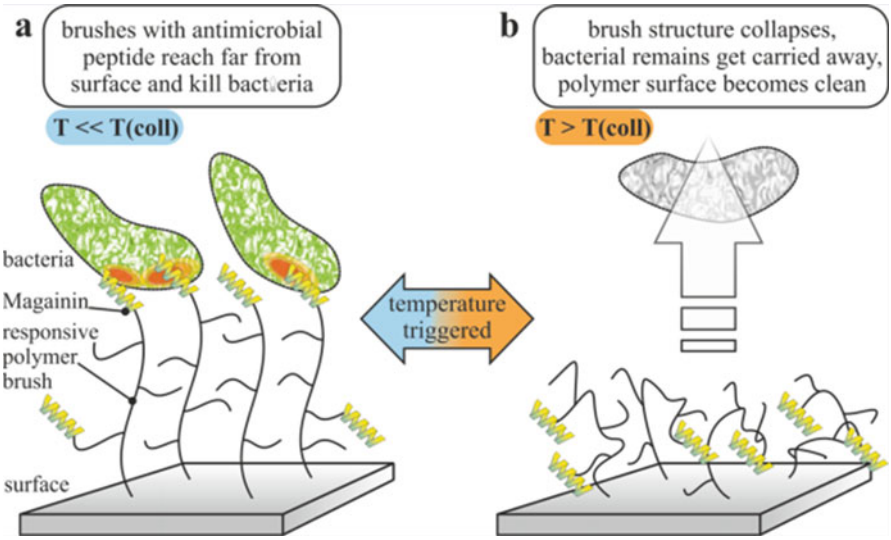


Fig. 5.7 Double contact-killing and repelling surfaces. Magainin grafted via thermoresponsive oligo(ethylene glycol) methacrylates (OEGMA) are able to (**a**) kill bacterial cells below and (**b**) repel them above the transition temperature. Reproduced with permission from [118]

5.6.3 Releasing and Contact-Killing

Biser et al. [24] developed a coating based on cellulose with an antimicrobial *N*,*N*-dimethyl-dodecylammonium (DDA) group grafted via poly(2-ethyl-1,3-oxazoline) ($PEtO_x$). The system worked as follows. First, the immobilized antimicrobial was able to kill approaching microbial cells on contact. The dead microbial cells deliver cellulose to the environment. Second, the liberated cellulose is capable of degrading the cellulose coating and reactivated the antibacterial activity again (Fig. 5.9). As major advantages over previous strategies, the authors mentioned that the cellulose-based coating reported can act as a contact-active system, is biologically compatible, degradable, and additionally might release biocides in case of a biological contamination only.

5.7 Responsive Antibacterial Surfaces

Modification of the surface with stimuli-responsive polymers has also been evaluated to make surfaces "antibacterial" [120]. As has been already mentioned, in general, previous designs of antibacterial surfaces resort to the delivery of antibiotics, antibacterial agents, or inorganic nanoparticles. Some of these strategies resulted in

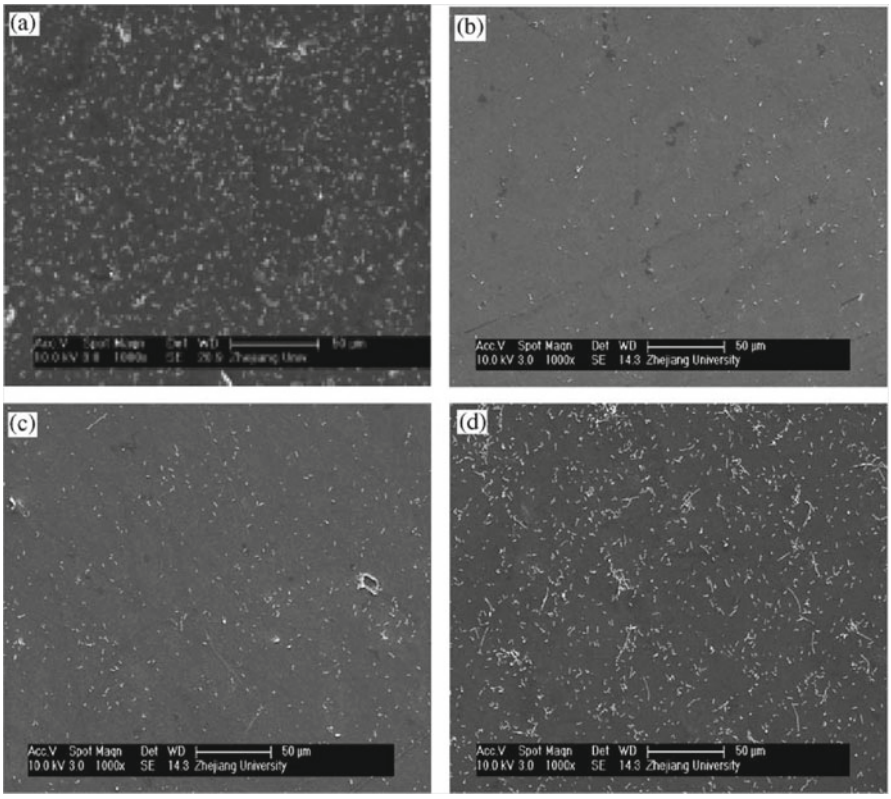


Fig. 5.8 Scanning electron micrographs of (**a**) pristine PET, (**b**) the (heparin/chitosan)$_6$ multilayer film assembled at pH = 2.9, (**c**) the (heparin/chitosan)$_6$ multilayer film assembled at pH = 3.8, and (**d**) the (heparin/chitosan)$_6$ multilayer film assembled at pH = 6.0 after exposure to 5×10^7cells = mL *E. coli* for 4 h. Reproduced with permission from [119]

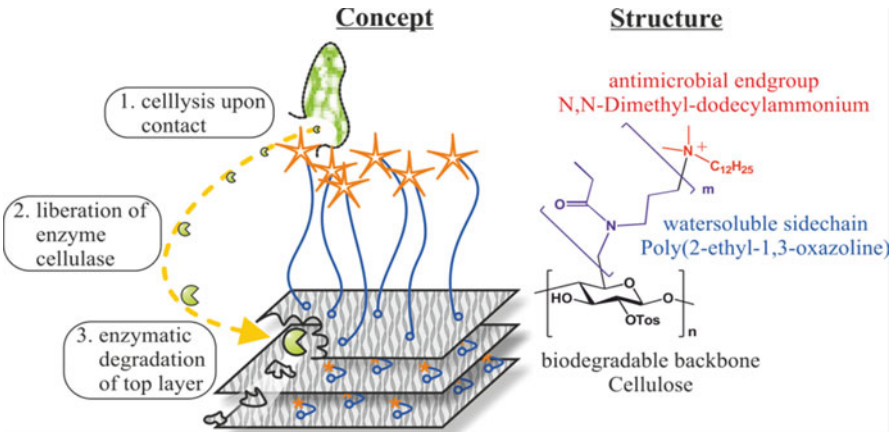


Fig. 5.9 Concept of contact-killing and releasing using a cellulose-based coating with an attached biocidal polymer. The cellulase deliver upon microbial killing can degrade the coating. Reproduced with permission from [24]

the increase of bacterial resistance, toxicity, or even the development of inflammatory responses. As a consequence, different studies evidenced the interest of designing novel antimicrobial coatings that respond only when infection occurs thus limiting the negative side effects. In general, these systems involve first the encapsulation of antimicrobial agents inside of the responsive thin coating. In a second step, using an external stimulus (temperature, pH, etc.) the antimicrobial agent is released [120]. As will be depicted, in other cases, the antimicrobial is covalently linked and they are exposed or hidden depending on the environmental conditions.

5.7.1 *Thermoresponsive Surfaces*

For instance, thermosensitive antimicrobial surfaces induce an increase or a decrease of the bacterial adhesion depending on the environmental temperature. Thermosensitive antimicrobial coatings reported by Laloyaux et al. [118] were able to switch from bactericidal for ambient storage conditions to passive in vivo. They prepared thermoresponsive coating formed by polymer brushes of copolymers based on 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA) and oligo(ethylene glycol) methacrylate (OEGMA). Moreover, an antimicrobial peptide, Magainin-I active against Gram-positive and Gram-negative bacteria [121, 122] was grafted on the hydroxyl groups of the brush. As depicted in Fig. 5.10, the structure of the

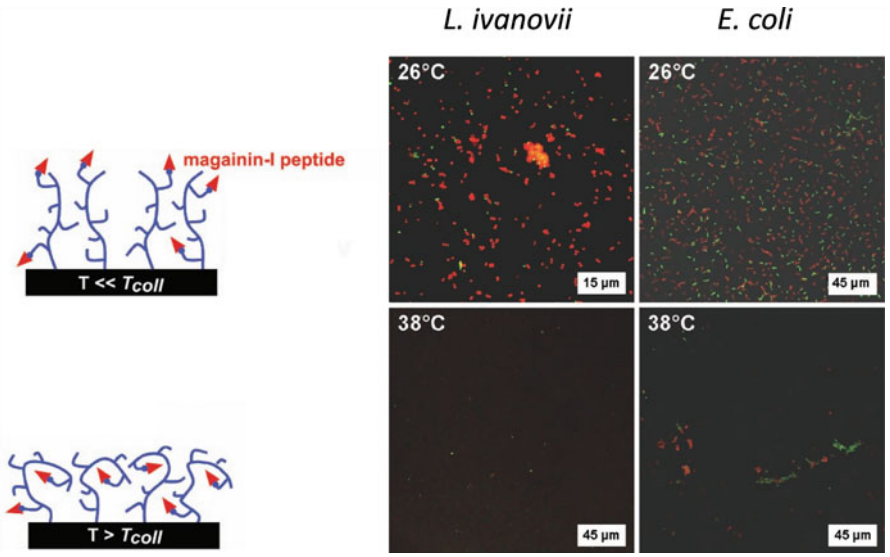


Fig. 5.10 (*Left*) Schematic drawing of the brush conformations below and slightly above LCST (T_{coll}). (*Right*) (MAG-Cys)-functionalized P(MEO_2MA_{50}-$HOEGMA_{20}$-$HEMA_{30}$) brush incubated in the presence of *L. ivanovii* or *E. coli* and subsequently stained with the LIVE/DEAD viability kit; samples incubated at 26 °C (*top*) and 38 °C (*down*). Reproduced with permission from [118]

temperature-responsive copolymer brushes based on oligo(ethylene glycol) methacrylates can be modified depending on the temperatures producing significant changes in the adhesion against various bacteria. The brushes switch from bactericidal to cell-repellent below and slightly above 35 °C, respectively, due to the progressive vertical collapse of the brush.

Pangilinan et al. [123] developed carbon nanotube (CNT)/PNIPA brush films exhibiting thermodependent antimicrobial action. They prepared the temperature-responsive carbon nanotube (CNT)/poly(*N*-isopropylacrylamide) (PNIPAM) hybrid brush films by combining the layer-by-layer and surface-initiated polymerization (LbL-SIP) techniques and evaluated the antimicrobial activity against *Exiguobacterium* sp. AT1b and Exiguobacterium sibiricum strains. The authors observed that CNT films showed antimicrobial action independently of the external temperature. On the contrary, CNT–PNIPAM films have antibacterial properties below 32 °C, which is below the lower critical solution temperature (LCST), but allows biofilm formation above the LCST.

5.7.2 pH-Responsive Surfaces

pH has been equally employed in the fabrication of smart antibacterial surfaces with on-demand switchable behaviors. For instance, Wei et al. [124] reported the fabrication of silicon nanowire arrays modified with a pH-responsive polymer, poly(methacrylic acid). This polymer has two main tasks. First, serves as a dynamic reservoir for the controllable loading and release of a natural antimicrobial lysozyme. Moreover, it works as self-cleaning platform for the release of dead bacteria and the reloading of new lysozyme thus enabling a repeatable use. Interestingly, using this strategy, the functionality of the surface can be simply switched via stepwise modification of the environmental pH and can be effectively maintained after several kill/release cycles.

5.7.3 Bioresponsive Surfaces

Bioresponsive materials refer to those interfaces that exhibit changes in response to enzymes or other constituents of the biological fluid or environment [125]. An extensively employed methodology to prepare antimicrobial surfaces takes advantage of biodegradable polymers charged with the appropriate active molecule. Some illustrative examples of biodegradable polymers employed in the fabrication of bioresponsive surfaces are depicted in Table 5.5.

Another strategy to prepare bioresponsive surfaces concerns the design of enzyme-responsive surfaces [120], where enzymes act on specific bonds that are activated in order to deliver the antimicrobial [140, 141]. In an illustrative report, Baier et al. [140] take advantage of this strategy to release an antimicrobial agent

Table 5.5 Biodegradable polymers and active molecules employed in the elaboration of antimicrobial bioresponsive surfaces

Biodegradable polymer	Active molecules	Reference
Polyphosphazenes	Ciprofloxacin and Norfloxacin	[126]
DL-dilactide polymer	Ciprofloxacin and Pefloxacin	[127]
Diisopropylcarbodiimide/poly (e-caprolactone)diol	Loaded with Nalidixic acid and Nalidixic acid derivatives	[128]
Poly(lactide-*co*-caprolactone)	Ciprofloxican-loaded biodegradable microsphere	[129]
1,6-Hexane diisocyanate/polycaprolactonediol polymers	Films of Ciprofloxican loaded	[130]
Chitosan have been shown to inhibit fungal and bacterial growth	Biodegradable composite films	[131–138]
Poly(lactic-*co*-glycolic acid) (PLGA)	Collagen	[139]

based on the action of an enzyme. In particular, they employed hyaluronic acid-based polymers that are known to be cleaved by enzymes called hyaluronidases. They designed and fabricated hyaluronic acid nanocapsules containing the antimicrobial polymer polyhexanide. The capsules were cleaved by enzymes and allow for polyhexanide release.

Using a similar approach, Tanihara et al. [141] reported the fabrication of a thrombin-sensitive peptide linker. Based on the fact that the presence of *S. aureus* in a wound is accompanied by increased thrombin-like activity and taking advantage of the fact that thrombin cleaves fibrinogen, these authors prepared fibrinogen-based thrombin-sensitive peptides. These peptides served as bridges between a hydrogel and a particular antibiotic. As a result of the cleaving of the thrombin-sensitive peptide, the antibiotic could be released to the environment.

Another strategy to prepare bioresponsive surfaces has been reported by Cavallaro et al. [120]. They proposed the fabrication of surfaces that contain partially exposed enzymes or coatings that leach-specific enzymes capable of protecting the surfaces from biological contamination or having antimicrobial effect [142–144]. This approach was employed by Wu et al. [142] that functionalized surfaces with exposed enzyme granules. The latter were able to protect them from various contaminations.

Finally, Satishkumar et al. [144] evaluated the in vitro antimicrobial activity of hernia repair meshes coated by the antimicrobial enzyme lysostaphin at different initial concentrations. In this study, the authors evidenced that leaching of lysostaphin significantly decreased the *S. aureus* infection within rat models. The antimicrobial activity of the lysostaphin-coated meshes suggests that such enzyme-leaching surfaces could be efficient at actively resisting initial bacterial adhesion and preventing subsequent colonization of hernia repair meshes.

5.7.4 *Other Responsive Interfaces*

Other stimuli have been equally employed to activate surfaces rendering them antimicrobial. These include the use of light onto photoactive surfaces, counterion-assisted modulation to facilitate the bacterial release or the fabrication of salt-sensitive surfaces.

Photoactive surfaces change their properties by variation of light wavelength, polarization, or light intensity. In this context, photodynamic antimicrobial chemotherapy (PACT) offers an alternative for the inactivation of pathogenic microorganisms based on the "photodynamic effect." In this approach, a photosensitizer, preferentially associated with a microorganism, is activated with nonthermal visible light of appropriate wavelength(s) to generate toxic species that inactivate the microorganism [145]. Upon absorption of a photon, such agents are able to release reactive oxygen species (ROS). Typically, reactive oxygen species can be generated in two forms: superoxide anions or hydroxyl radicals (type I) or singlet oxygen (type II) [146, 147]. The reactive radicals released from such coatings target bacteria in a non-site-specific manner. Unlike site-specific antimicrobial agents, i.e., antibiotics, it is difficult for bacteria to develop resistance to non-site-specific antimicrobials [147].

Photochemistry has revealed that both inorganic photocatalysts and organic photosensitizers could generate some reactive oxygen species (ROSs) on certain polymeric surfaces under light exposure, and these ROS can provide antimicrobial and decontaminating functions. Thus, researchers have been trying to incorporate the photoactive agents into various polymeric substrates to prepare self-decontaminating materials for medical applications, protective clothing, etc. [148].

Organic photosensitizers [145] employed as antimicrobials include phenothiazinium-based photobactericidal materials such as methylene blue (MB) or toluidine blue O (TBO), ruthenium complexes, rose Bengal, or phthalocyanines. These have been successfully employed for the inactivation of various Gram (+) and Gram (−) bacteria [149], such as Escherichia coli [150, 151], Staphylococcus aureus [151, 152], Streptococcus mutans [153], Porphyromonas gingivalis [154], and Pseudomonas aeruginosa [152, 155], have been documented in the literature.

Other alternative explored involves the use of UV irradiation on TiO_2-based coatings that are able to destroy cancer cells, bacteria, viruses, and algae [156]. For instance, Tallosy et al. [157] prepared photocatalysts (nanosilver-modified TiO_2 and ZnO photocatalysts)/polymer nanohybrid films by spray coating on the surface of glass plates. The photoreactive surfaces were activated with visible light emitting LED at $l = 405$ nm. The antibacterial effect of the nanohybrid films was evidenced by measuring the decrease of the S. aureus amount on the surface as a function of illumination time. The authors evidenced that the photocatalyst/polymer nanohybrid films could inactivate 99.9 % of the investigated bacteria on different thin films after 2 h of illumination with visible light source. In a recent example, Charpentier et al. [158] synthesized nano-titania/polyurethane ($nTiO_2$/polyurethane) composite coatings, where $nTiO_2$ was chemically attached to the backbone of the polyurethane

polymer matrix. The functionalized $nTiO_2$-polyurethane composite coatings showed excellent antibacterial activity against Gram-negative bacteria Escherichia coli; 99 % of E. coli were killed within less than 1 h under solar irradiation.

TiO_2 have been employed in the elaboration of other composites using PP [159], nylon [160], PS [161], or PMMA [162] as polymer matrices.

Counterion-activated nanoactuators permit to reversibly kill/release bacteria. Huang et al. [163] reported an strategy to release attached bacteria from surface-grafted bactericidal poly((trimethylamino)ethyl methacrylate chloride) (pTMAEMA) brushes. They prepared pTMAEMA brushes by surface-initiated atom transfer radical polymerization, and the surfaces were washed with electrolyte solutions containing anions with different lipophilic characteristic, charge density, polarity, and adsorbility to quaternary ammonium groups in polymers. Because of the special ion-pairing interactions, the interfacial properties, including wettability and ζ-potential, can be manipulated in a controlled manner. As a result, the counterion-assisted modulation of pTMAEMA brushes facilitates the bacterial release and regeneration of antimicrobial polymer films.

Finally, as demonstrated by Yang et al. [164] also the salt concentration can play a key role on the antifouling properties. They fabricated zwitterionic poly(3-(1-(4-vinylbenzyl)-1H-imidazol-3-ium-3-yl)propane-1-sulfonate) (polyVBIPS) brushes as ion-responsive smart surfaces via the surface-initiated atom transfer radical polymerization. They examined the salt-response and evaluated the variation on the surface hydration and as a consequence on both friction, and antifouling properties. In particular, they compared both in water and in salt solutions with different salt concentrations and counterion types. According to the authors, the polyVBIPS brushes exhibited reversible surface wettability switching between in water and saturated NaCl solution. As a result, polyVBIPS brushes in water induced larger protein absorption, higher surface friction, and lower surface hydration than those in salt solutions. Interestingly, at appropriate ionic conditions, polyVBIPs brushes were able to switch to superlow fouling surfaces (<0.3 ng/cm^2 protein adsorption) and superlow friction surfaces ($u \sim 10^{-3}$).

5.8 Conclusions

This chapter depicts the multiple strategies reported to reduce or to completely avoid bacterial contamination onto polymeric surfaces. As has been shown, surface modification is crucial in order to achieve this goal. In this context, different strategies can be employed.

Grafting approaches or the deposition of coatings onto the surfaces have been extensively employed to reduce the bacterial adhesion. More recent strategies resort to responsive materials. Temperature, pH, UV-light, or even salt has been demonstrated to be interesting stimuli that can produce the bacterial detachment in a precise manner.

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