Review

Combating medical device fouling

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When interfaced with the biological environment, biomedical devices are prone to surface biofouling due to adhesion of microbial or thrombotic agents as a result of the foreign body response. Surface biofouling of medical devices occurs as a result of nonspecific adhesion of noxious substrates to the surface. Approaches for biofouling-resistant surfaces can be categorized as either the manipulation of surface chemical functionalities or through the incorporation of regulatory biomolecules. This review summarizes current strategies for creating biofouling-resistant surfaces based on surface hydrophilicity and charge, biomolecule functionalization, and drug elution. Reducing the foreign body response and restoring the function of cells around the device minimizes the risk of device rejection and potentially integrates devices with surrounding tissues and fluids. In addition, we discuss the use of peptides and NO as biomolecules that not only inhibit surface fouling, but also promote the integration of medical devices with the biological environment.

Device rejection: common reasons leading to failure

Medical devices (see Glossary) play a key role in the treatment of ailments and are meant to substitute, and in some cases restore, biological function. However, the inclusion of synthetic materials used for orthopedics, catheters, infusion lines, vascular stents and grafts, and sutures into a biological environment triggers a foreign body response. The foreign body response to artificial materials often results in biofouling, thereby limiting the clinical lifetime of the device. Furthermore, the increasing use of invasive medical procedures for the implantation of devices leads to an increased risk for the development of device-associated infections. Current estimates place the occurrence of bacterial-related infections for humans at 65%, and are associated with the growth of bacterial biofilms on device surfaces [1]. The combination of surface thrombus and biofilm formation that eventually inhibits the functionality of the device is collectively termed biofouling [2–6]. Severe biofouling of medical devices, ultimately resulting in failure, is only effectively corrected by the removal and replacement of the device through costly invasive procedures. Given the broad scope of medical device use and the physiological environments to which they are exposed makes the design of antifouling materials a challenge requiring multiple avenues of approach.

In order to design materials that can combat the negative effects associated with surface biofouling, we must first consider the process involved [7]. Although the exact mechanisms of attachment of biological agents to the surface of medical devices is not well understood, physical and chemical surface properties are known to influence the type and extent of surface fouling [8]. Upon insertion into a liquid environment, a conditioning layer immediately forms, composed of lipids and glycoproteins, on the device surface. The composition of the conditioning layer is dictated by the device surface properties, including charge and hydrophilicity, and environmental factors such as pH and temperature. The composition of the conditioning layer subsequently influences what types of bacterial strains can colonize the surface and the likelihood of thrombus formation [8]. Once a suitable environment for attachment is established, bacterial species are capable of adhering to the surface and proliferating into microcolonies, eventually forming biofilms. Biofilms found on blood-contacting devices often include a large portion of host clotting proteins and immune cells intended to isolate the infection and prevent the formation of sepsis [5,6].

Bacterial biofilms are encased in a protective shield of exopolysaccharides, which increases the resistance of bacteria to antimicrobial agents 1000-fold compared to bacteria growing in suspension [8,9]. As a result, the failed immune response results in the additional accumulation of biomolecules on the device surface, accentuating the formation of thrombus [5,10]. The surface biofouling results in loss of device function, ranging from obstruction to damaging surrounding healthy tissues (Figure 1). Ultimately, mature biofilms detach from the surface of the device and

Glossary

Biocompatible: denotes a material that does not illicit an adverse response when interfaced with a host environment.
Biofilm: a complex assembly of microorganisms and proteins that are attached to the surfaces of medical devices, which interfaces with the biological environment.
Biofouling: chronic formation of a biofilm on a medical device surface, causing the function of the device to be impaired.
Medical device: a material form, intended to serve a mechanical and physiological function, which is interfaced in a biological system.
Thrombus: aggregation of proteins and platelets on a surface that results in the formation of a blood clot.
Zwitterion: a neutral molecule that contains both positive and negative charges.

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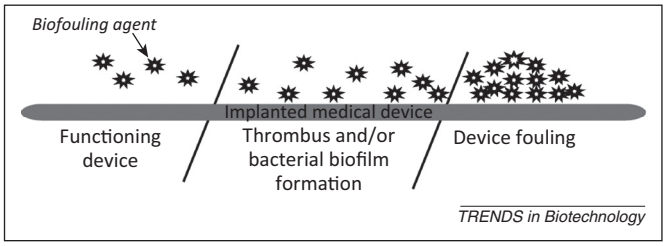

Figure 1. Surface biofouling of an implanted medical device due to the adhesion of bacterial colonies and/or thrombolytic agents.

are released as infectious boluses or dangerous emboli associated with life-threatening complications [8,11].

Materials design for resisting biofouling

Maintaining medical devices in a homeostatic environment with the biological interface is key to their sustained usage. Complications associated with fouled medical devices are often costly to repair for both the patients and caretakers. According to the old adage, 'an ounce of prevention is worth a pound of cure', the fabrication of biomaterials for medical devices has turned towards the development of materials that can inhibit surface biofouling. The design of next-generation biomedical devices is primarily aimed at preventing surface fouling through passive and active approaches by the manipulation of physical and chemical surface properties, respectively (Figure 2). The fabrication of materials is designed as antiadhesive, based on their ability to prevent the adhesion of noxious biomolecules, or antimicrobial by denaturing infectious microbes and subsequently restricting the proliferation of biofilms. Antimicrobial materials can be designed as either passive or active materials. Manipulation of surface properties to construct a passive antimicrobial surface primarily includes functionalization of the surface with antimicrobial peptides (Figure 2E), which not only neutralizes the pathogen, but also prevents the adhesion and subsequent formation of surface biofilms. Active approaches towards antimicrobial action primarily rely on drug-eluting materials that neutralize pathogens, but only minimally inhibit surface adhesion. Ideally, a biomedical device will facilitate antifouling behavior while supporting the integration of the medical device into a homeostatic state with the surrounding environment. In this review, we provide a summary of each technique used for resisting surface fouling and also present the concerted approach that aims for the integration of biomaterials with surrounding tissues and fluids.

Passive materials for resisting biofouling

Hydrophilic surfaces

Hydrophilic low-fouling and nonfouling surfaces share common structural and chemical properties such as electrical neutrality and the capacity to form hydrogen bonds [12]. Hydrophilic surfaces resist the adhesion of fouling agents to the material surface through the formation of a physical barrier known as a hydration layer [12,13]. The hydration layer is formed as a result of hydrogen bonding between the functional groups on the device surface and water molecules in the environment. The preparation of hydrophilic materials is achieved based on the inclusion of chemical functionalities capable of forming hydrogen bonds on the monomeric units of the polymer backbone [13]. The effectiveness of the hydrophilic materials is based on the strength of the hydration layer, which is dictated by the physiochemical properties of the material, including molecular weights of the polymer and the conformation of the polymer chains.

The current gold standard material in the preparation of biomedical devices is polyethylene glycol (PEG) [14]. PEG is an intrinsically low-fouling surface capable of resisting nonspecific protein adsorption and cell adhesion due to the formation of hydration layer with the surrounding environment. Alternative antifouling materials with an improved resistance to a loss of function currently under consideration are polyamides, polyurethanes, and naturally occurring polysaccharides, including chitosan and dextran [13,15]. Combinatorial synthesis of various monomer units incorporating a range of functional groups for the construction of superior hydrophilic antifouling surface are also under exploration. However, prolonged exposure of hydrophilic materials in a biological environment results in the destruction of the hydration layer, due to surface oxidation that inhibits the antifouling properties [13].

Hydrophobic surfaces

Rather than relying on the formation of a relatively labile hydration layer, hydrophobic materials are designed to repel the attachment of water and biomolecules alike. Hydrophobic materials are prepared by incorporating functional groups that resist hydrogen bonding onto the surface of the material. Medical devices with hydrophobic surfaces in the past were considered toxic to the host environment due to the inclusion of toxic components in materials coatings needed to render the surface hydrophobic. Recently, biocompatible fluorinated hydrophobic coatings have been reported using silica colloids [16] or through the deposition

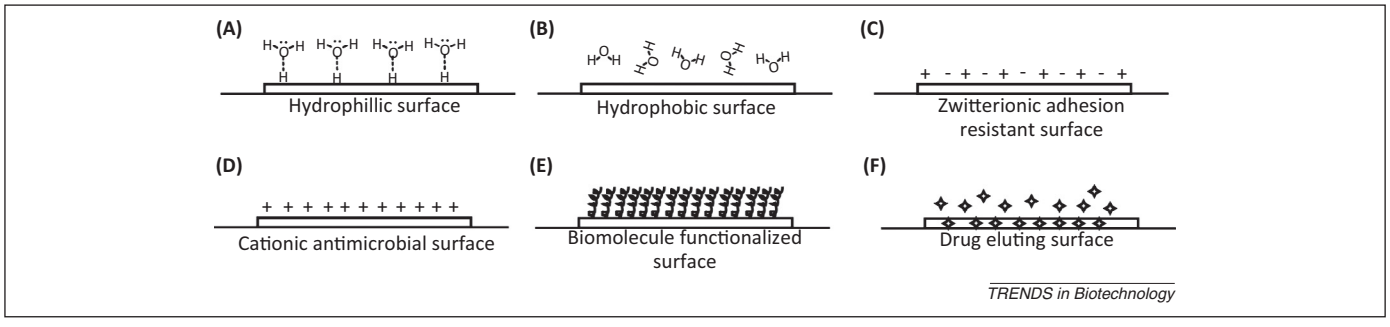

Figure 2. Surface modification methods for combating device surface fouling using passive **(A–E)** and active **(F)** approaches. These approaches rely on the development of adhesion-resistant coatings (A–C, F) and surfaces with antimicrobial properties (D–F).