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Engineering biomaterials surfaces to modulate the host response

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ABSTRACT

Undesirable host response is responsible for the surface induced thrombus generation, activation of the complement system and the inflammatory reactions by the blood-contacting biomaterials. The surface interaction of biomaterials with different blood components is thought to be the critical factor that dictates the host response to biomaterials. Surface engineering can be utilized as a method to enhance the biocompatibility and tailor the biological response to biomaterials. This review provides a brief account of various polymer brush based approaches used for biomaterials surface modification, both passive and bioactive, to make the material surfaces biocompatible and antibacterial. Initially we discuss the utilization of polymer brushes with different structure and chemistry as a novel strategy to design the surface non-fouling that passively prevent the subsequent biological responses. Further we explore the utility of different bioactive agents including peptides, carbohydrates and proteins which can be conjugated the polymer brush to make the surface actively interact with the body and modulate the host response. A number of such avenues have also been explored in this review.

1. Introduction

The use of biomaterials has profoundly changed the modern medicine. Biomaterials have found number applications in drug delivery, tissue engineering, devices and as implants [1–3]. Many of these biomedical materials will come in contact with blood at some point in their use and the interactions with blood components play a vital role in their optimal performance. Extensive research and development over the last several decades addressed some of the issues, however problems still exist owing to the non-specific protein adsorption, thrombus generation due to the activation of coagulation cascade, activation of the complement system and inflammatory reactions [4–7]. In addition, the biomaterials-associated infection results in significant complications [8]. The interplay between these biological reactions on biomaterials surface (Fig. 1) results in the formation of a transient provisional matrix and the onset of chronic inflammatory responses results in poor performance of biomaterials and devices. The mechanism of many of these reactions and cross-talk between different players are poorly understood and varies with the type of materials used. Addressing these challenges is critical to tailor and optimize the performance of the materials both for short term and long term use.

The surface interaction of the biomaterials with different blood components is thought to be the critical factor that dictates the host response to biomaterials especially those used in blood-contacting applications [9,10]. Thus surface engineering can be utilized as a method to increase the biocompatibility and tailor the biological response to biomaterials, and this approach is gaining lot of interest in recent years. Such surface coatings can be designed to be either 'passive or inert' or that can interact specifically with endogenous players in body to provide specific functions in vivo 'active biomaterials' for the optimal function of devices and implants (Fig. 2). Among the surface modification techniques, the coatings based on polymer brushes, one end tethered polymer chains on the surface at high density, have emerged as a platform technique to tailor the surface properties of the materials [11,12]. The advantage of such nano-structured coating include, the stability of the grafted polymer layer owing to the covalent grafting, functionality of the surface provided by the grafted polymer chains, and potential application of the technique to a variety of biomedical surfaces including metals, plastics and ceramics. In this review, we highlight recent advances in the development of coatings for blood-contacting biomaterials focusing on the surface coating that passively or actively reduce thrombus generation, modulate immune response and prevent bacterial infection.

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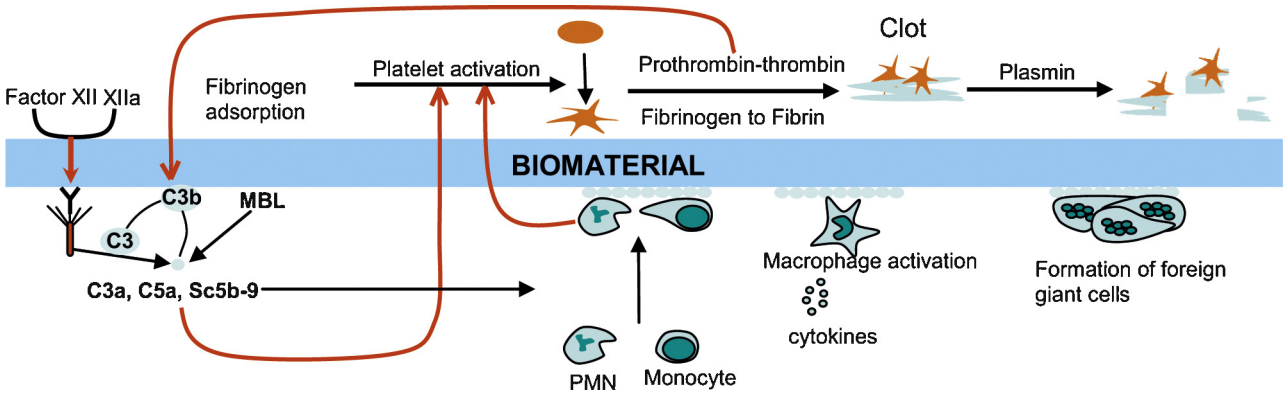

Fig. 1. *Coagulation cascade*: contact activation of factor XII to XIIa and adsorbed fibrinogen on biomaterials surface induces platelet activation. Activated platelets catalyze clot formation by converting prothrombin into thrombin, which then cleaves fibrinogen into fibrin for the formation of the blood clot. The clot will be lysed slowly by the fibrinolytic system. Plasmin lyses the fibrin clot resulting in fibrin degradation. *Activation of complement system*: Conformational changes of complement proteins, adsorption of IgG, MBL and MSP2 could induce activation of the complement system on a biomaterial surface via the classical, alternative and lectin pathways. Due to lack of self-recognition, the complement activation rapidly amplified and generates C3a and C5a anaphylatoxins that recruit polymorphonuclear leukocytes (PMNs) and monocytes onto the biomaterial surface. This also results in integrin-receptor-mediated leukocyte adhesion and activation. The bound monocyte then differentiated to macrophage. Adherent macrophages on biomaterials become activated in an attempt to phagocytose the biomaterial. Individual macrophages consequently fuse to form foreign-body giant cells. The complement and the coagulation cross-talk occur through multiple interactions (indicated by red arrows). Activated clotting Factor XII (FXIIa) can activate the classical complement pathway through C1 cleavage. Thrombin directly cleave complement component C3 and C5 and generates biologically active C5a. C5a and SC5b-9 activate platelets, neutrophils and endothelial cells. The activated leukocytes on the biomaterials surface can induce activation of the attached platelet. All these reactions at biomaterial surface directs the inflammation and the healing process. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

2. Antithrombotic coatings

Biomaterial induced thrombus generation is a major clinical concern associated with medical devices such as coronary stents, heart valves, catheters, vascular grafts, extracorporeal tubing, hemodialysis membranes and glucose sensors [13–15]. When blood flows through a medical device or an implant, non-specific protein adsorption at the biomaterial interface is the first and critical event that initialize a cascade of host responses, including platelet adhesion and activation, initiation of coagulation cascade, finally the thrombus generation and this will be followed by the remodeling of the blood clot by the fibrinolytic system (Fig. 1) [4,9]. The contact activation pathway of blood coagulation cascade is thought to be involved in the initiation of such events. Thus control of such process without excessive surface induced coagulation activation or local enhancement in the endogenous fibrinolytic activity [16,17] is important to prevent the formation of thrombus on material surfaces. Many different strategies are experimented.

2.1. Passive surface coatings

An essential feature of biomaterials used for implanted device is their biological inertness. The main purpose of developing biologically inert coatings was to reduce unfavorable host response to a foreign surface. Inert "non-fouling" polymer brushes have been considered as passive coatings and applied on surfaces to reduce the non-specific protein adsorption and cell attachment. Preventing or minimizing the adsorption of early players in contact activation pathway of blood coagulation is thought to prevent thrombus generation. Densely grafted hydrophilic polymer brush can function as an inert shielding layer, or "barrier," to reduce the undesirable interactions between the surface and the biological fluid [18]. The

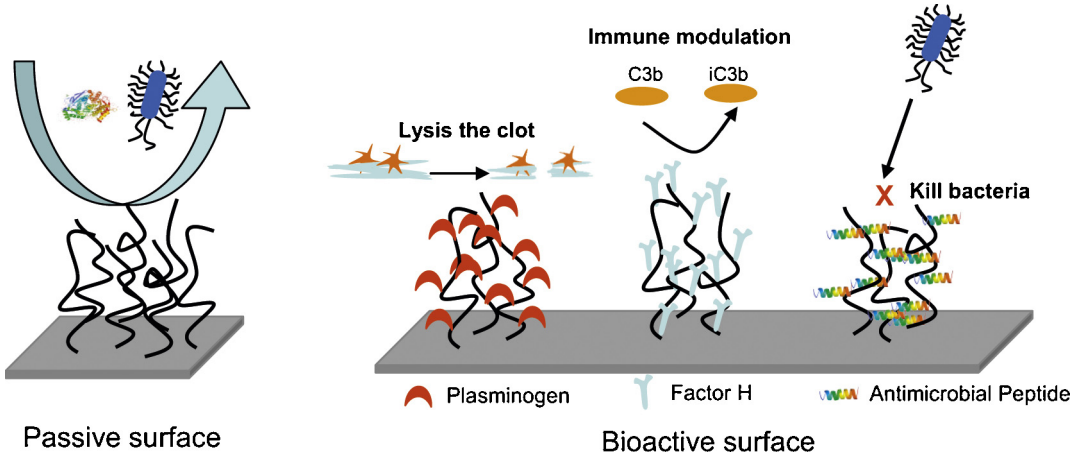

Fig. 2. Modification of the biomaterials surface with polymer brushes *passively* protect against protein or bacteria adhesion to prevent the undesired response. The interaction of protein or bacteria with densely grafted polymer chains in the brush form gives rise to a free energy penalty owing to already stretched chain conformation of the brush system. The increased energy level disfavors the adsorption of protein or bacteria onto the brush surface which becomes the driving force for protein repelling characteristics of the polymer brush. Or the surface can *actively interact* with the biological system by the presence of bioactive agents on polymer chains. For example, plasminogen can be coupled into the brush and facilitate the lysis the blood clot. Factor H can be conjugated into the brush and modulate the immune response by deactivating C3b to iC3b. Antimicrobial peptides can be incorporated into the brush to kill bacteria adhered onto the surface.