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Surface tailoring for selective endothelialization and platelet inhibition via a combination of SI-ATRP and click chemistry using Cys–Ala–Gly-peptide

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ABSTRACT

Surface tailoring is an attractive approach to enhancing selective endothelialization, which is a prerequisite for current vascular prosthesis applications. Here, we modified polycarbonate urethane (PCU) surface with both poly(ethylene glycol) and Cys–Ala–Gly-peptide (CAG) for the purpose of creating a hydrophilic surface with targeting adhesion of endothelial cells (ECs). In the first step, PCU-film surface was grafted with poly(ethylene glycol) methacrylate (PEGMA) to covalently tether hydrophilic polymer brushes via surface initiated atom transfer radical polymerization (SI-ATRP), followed by grafting of an active monomer pentafluorophenyl methacrylate (PFMA) by a second ATRP. The post-polymerization modification of the terminal reactive groups with allyl amine molecules created pendant allyl groups, which were subsequently functionalized with cysteine terminated CAG-peptide via photo-initiated thiol-ene click chemistry. The functionalized surfaces were characterized by water contact angle and XPS analysis. The growth and proliferation of human ECs or human umbilical arterial smooth muscle cells on the functionalized surfaces were investigated for 1, 3 and 7 day/s. The results indicated that these peptide functionalized surfaces exhibited enhanced EC adhesion, growth and proliferation. Furthermore, they suppressed platelet adhesion in contact with platelet-rich plasma for 2 h. Therefore, these surfaces with EC targeting ligand could be an effective anti-thrombogenic platform for vascular tissue engineering application.

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1. Introduction

The interaction of artificial biomaterials with blood usually causes a number of thrombogenic and inflammatory reactions when the blood is exposed to the extracellular matrix (ECM) of a disrupted vessel [1]. Many strategies have been developed to prevent these reactions, such as rapid endothelialization onto biomaterial surface. For this purpose, the adhesion, proliferation and migration of endothelial cells (ECs) should be mediated or enhanced by special peptides, vascular endothelial growth factor (VEGF) and genes [2,3]. Furthermore, endothelialization on artificial vascular graft surface is essential in order to maintain vessel integrity, which could provide an effective technique to prevent in-stent restenosis (ISR) and late stent thrombosis (LAST) [4]. ECs are responsible for proper functions of coronary arteries, tightly controlling the migration and proliferation of smooth muscle cells (SMCs) and inhibiting platelet activation inside the blood. Recently the drug-eluting stents have been demonstrated to reduce the proliferation and migration of SMCs. However, these stents might suffer from a fatal disadvantage of inhibitory effect on endothelialization, which retards the healing process and results in a high rate of LAST [5].

Polycarbonate urethanes (PCUs) have recently made a rapid progress for cardiovascular and other biomedical applications because of their excellent elasticity, strength, durability and tolerance in body during the healing process [6–10]. However, PCUs have some limitations, such as high hydrophobic nature, and unsatisfactory or nonspecific cell adhesion and proliferation, which

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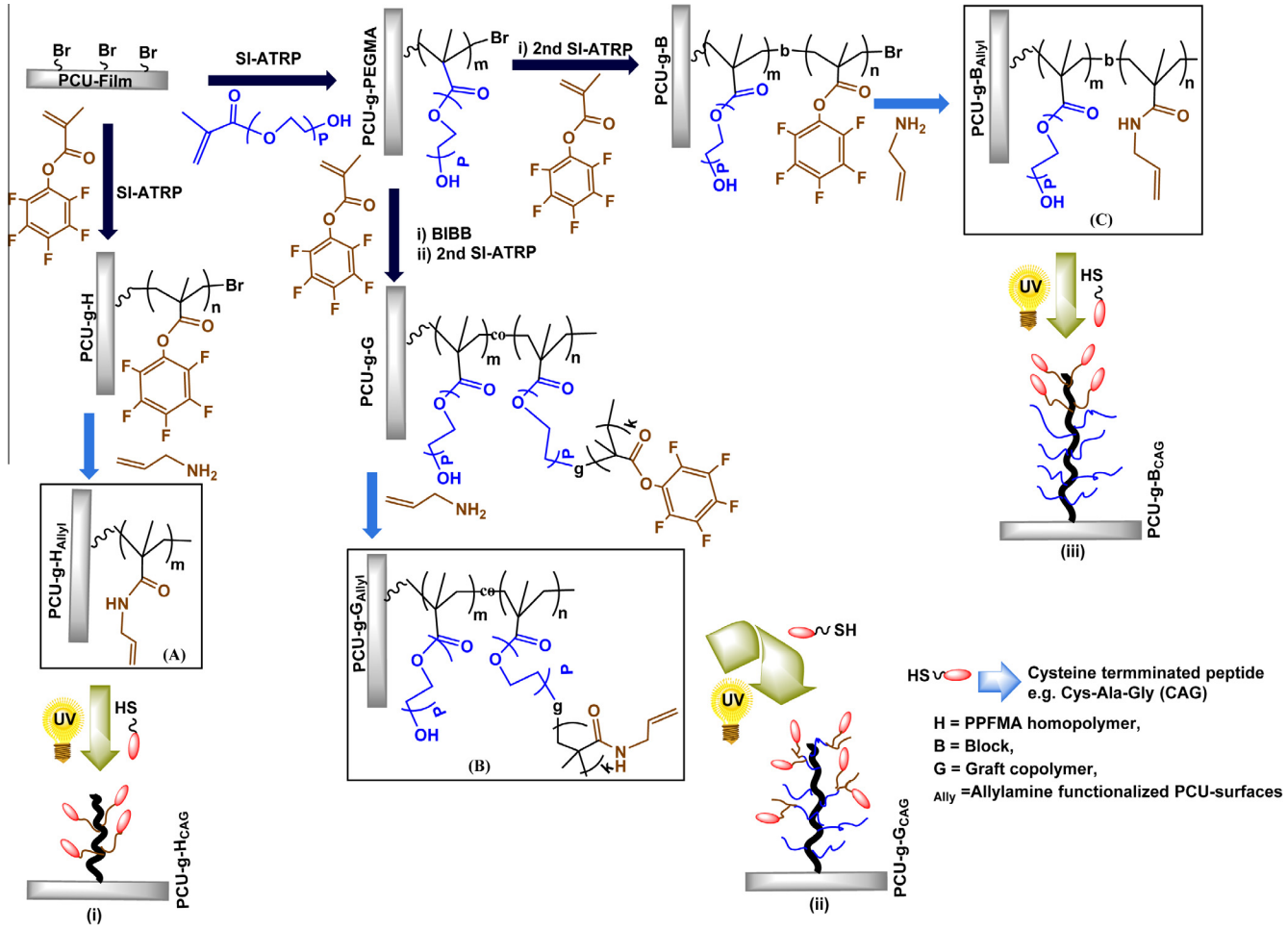
have confined their application in tissue engineering [11–14]. To circumvent these obstacles, many surface modification approaches have been attempted to reduce the thrombogenic nature and enhance cell growth on the surface [15,16]. Thrombosis is originated by the adhesion of serum proteins, platelets and circulating blood cells on the inner-surface of damaged vascular vessels. Because of lacking sufficient ECs on artificial vascular graft surface, SMCs may excessively grow and result in neointimal hyperplasia. Both of these risks are related to the endothelial damage [17].

Several natural and synthetic macromolecules, including gelatin, collagen, albumin, fibronectin derived peptide RGD [18], laminin derived-peptide YIGSR [19], cell adhesive peptides, VEGF, basic fibroblast growth factor (bFGF), and transforming growth factor (TGF-β1), have been used to functionalize the surface of vascular prostheses [20–24]. These biomimetic moieties composed of a variety of ECM components could synergistically provide an ideal environment for cell adhesion, growth and homeostasis [25].

Although the surfaces modified with these anti-thrombogenic molecules have been proved to enhance EC adhesion and proliferation [26], very little attention has been paid to the response of SMCs on these surfaces [27,28]. However, the specific promotion or competitive enhancement of ECs over SMCs on the designed surface plays an important role in the prevention of thrombosis and ISR [29]. To this end, the collagen type IV enriched peptide, Cys–Ala–Gly (CAG), has been utilized to selectively promote EC adhesion, but it exhibits a low adhesive tendency toward SMCs [17,30].

Among the established surface grafting techniques, surface initiated atom transfer radical polymerization (SI-ATRP) is a robust methodology that allows for the ultrafast polymer synthesis with controlled properties. Especially, SI-ATRP can create polymer brushes on various material surfaces [16,31–36]. Generally, the allyl side chains in vinyl monomers are not compatible with controlled radical polymerization because of the propensity of crosslinking reaction, which makes them less proficient for direct polymerization. On the other hand, utilizing the concept of post-polymerization modification of the active graft polymer brushes, such as poly(pentafluorophenyl methacrylate) (PPFMA), might be a more effective approach for biomolecule immobilization [37–39]. Thiol-ene click reaction is a convenient method for the immobilization of biomolecules, because of several advantages, such as, mild experimental conditions, high yield and rapid reaction rate [40–46]. The radical thiol-ene click reaction is an attractive technique for the conjugation of biological targets onto material surface [47,48,44,49–51].

In the present work, we developed a biomimetic functional surface on PCU film in order to prevent surface thrombosis. PEGMA was first polymerized onto PCU film to create the hydrophilic surface as background, subsequently grafting PFMA to introduce diblock polymer or graft polymer brushes onto the surface with the aim to provide many active sites (Scheme 1). We used low PFMA content in feed in order to provide only a few terminal groups for peptide functionalization, meanwhile preserve the antifouling properties of the surface. After postpolymerization



Scheme 1. Sequential grafting of PEGMA and poly(pentafluorophenyl methacrylate) (PPFMA) onto PCU surface by SI-ATRP to create PCU-g-H, PCU-g-G and PCU-g-B surfaces. The postpolymerization modification of them with allylamine to form (a) PCU-g-H_{Allyl}, (b) PCU-g-G_{Allyl} and (C) PCU-g-B_{Allyl} surfaces, while subsequent CAG-peptide functionalization by thiol-ene click reaction to prepare (i) PCU-g-H_{CAG}, (ii) PCU-g-G_{CAG} and (iii) PCU-g-B_{CAG} surfaces.

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