Direct thrombin inhibitor-bivalirudin functionalized plasma polymerized allylamine coating for improved biocompatibility of vascular devices

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ABSTRACT

The direct thrombin inhibitor of bivalirudin (BVLD), a short peptide derived from hirudin, has drawn an increasing attention in clinical application because it is safer and more effective than heparin for diabetic patients with moderate- or high-risk for acute coronary syndromes (ACS). In this study, BVLD was covalently conjugated on plasma polymerized allylamine (PPAam) coated 316L stainless steel (SS) to develop an anticoagulant surface. QCM-D real time monitoring result shows that 565 ± 20 ng/cm² of BVLD was bound to the PPAam surface. Infrared spectroscopy (IR) and X-ray photoelectron spectroscopy (XPS) confirmed the immobilization of BVLD. The conjugation of BVLD onto the PPAam coating led to enhanced binding of thrombin, and the activity of the thrombin adsorbed on its surface was effectively inhibited. As a result, the BVLD immobilized PPAam (BVLD-PPAam) substrate prolonged the clotting times, and exhibited inhibition in adhesion and activation of platelets and fibrinogen. We also found that the BVLD-PPAam coating significantly enhanced endothelial cell adhesion, proliferation, migration and release of nitric oxide (NO) and secretion of prostaglandin I2 (PGI2). In vivo results indicate that the BVLD-PPAam surface restrained thrombus formation by rapidly growing a homogeneous and intact endothelium on its surface. These data suggest the potential of this multifunctional BVLD-PPAam coating for the application not only in general vascular devices such as catheters, tubes, oxygenator, hemodialysis membranes but also vascular grafts and stents.

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1. Introduction

For the blood-contacting biomedical devices such as catheters, tubes, oxygenator, hemodialysis membranes, vascular stents or grafts, the activation of blood coagulation processes at their surfaces is an ongoing problem in medicine. Thrombin is the key enzyme of the plasmatic coagulation cascade, which is produced after vessel injury or blood contacting with a foreign surface. Besides fibrin formation, it enhances several reactions of the coagulation cascade in sense of a positive feedback loops and it activates blood platelets, leukocytes and endothelial cells. Thus to control thrombogenesis, this enzyme provides a predominant target [1].

Heparin is the most widely used anticoagulant drug to prevent blood clotting; its principle anticoagulant mechanism is the interaction with antithrombin III (ATIII), accelerating the inactivation of thrombin or other coagulation factors [2]. Heparin immobilization on biomaterial surfaces has drawn great attention due to its potential application in improving hemocompatibility [3–5]. However, heparin has several biological limitations, such as the risks of heparin induced osteopenia and thrombocytopenia (HIT) [6]. Moreover, heparin has a high affinity to bind with plasma proteins and cells (such as macrophages) and causes a nonlinear relationship between the anticoagulant effect and heparin dose [7]. Because thrombin plays a central role in thrombogenesis, the goal of most treatment regimens is to block thrombin generation or inhibit its activity. In contrast to heparin, direct thrombin inhibitors block directly the thrombin active site and consequently inhibit the activity of soluble thrombin and fibrin bound thrombin [8]. For these reasons, direct thrombin inhibitors were developed to