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Creation of a blood-compatible surface: A novel strategy for suppressing blood activation and coagulation using a nitroxide radical-containing polymer with reactive oxygen species scavenging activity

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ABSTRACT

Various polymeric materials have been used in medical devices, including blood-contacting artificial organs. Contact between blood and foreign materials causes blood cell activation and adhesion, followed by blood coagulation. Concurrently, the activated blood cells release inflammatory cytokines together with reactive oxygen species (ROS). We have hypothesized that the suppression of ROS generation plays a crucial role in blood activation and coagulation. To confirm this hypothesis, surface-coated polymers containing nitroxide radical compounds (nitroxide radical-containing polymers (NRP)) were designed and developed. The NRP was composed of a hydrophobic poly(chloromethylstyrene) (PCMS) chain to which 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) moieties were conjugated via condensation reaction of the chloromethyl groups in PCMS with the sodium alcoholate group of 4-hydroxy-TEMPO. Blood compatibility was investigated by placing NRP-coated beads in contact with rat whole blood. The amount of ROS generated on PCMS-coated beads used as a control increased significantly with time, while NRP-coated beads suppressed ROS generation. It is interesting to note that the suppression of inflammatory cytokine generation by NRP-coated beads was shown to be significantly higher than that by PCMS-coated beads. Both platelet and leukocyte adhesion to the beads were suppressed with increasing TEMPO incorporation in the polymer. These results confirm that the suppression of ROS by NRP prevents inflammatory cytokine generation, which in turn results in the suppression of blood activation and coagulation on the beads.

1. Introduction

Various materials are employed in blood-contacting implantable and extracorporeal medical devices, such as artificial hearts, artificial blood vessels, hemodialyzers and apheresis columns. Since most of those medical devices have poorly biocompatible surfaces, anticoagulants such as ethylenediamine tetraacetic acid (EDTA), hirudin, heparin, and warfarin are utilized to prevent thrombosis and embolism induced by contact between blood and these medical devices [1]. Given the side-effects of these anticoagulants, such as heparin-induced thrombocytopenia [2,3], however, numerous efforts have been made to reduce the activation of blood in response to contact with material surfaces. Suppression of such blood activation can effectively reduce the amount of anticoagulant required. In order to improve the blood compatibility of material surfaces, a number of versatile methods have been applied. One of the most simple and important techniques is polymer coating using biocompatible polymers such as poly(ethylene glycol) [4], zwitterionic polymers [5–7], microphase-separated polymers [8,9], and poly(2-methoxyethyl acrylate) [10]. These approaches can drastically reduce the adsorption of serum proteins. Protein adsorption triggers the activation of blood cells and blood coagulation on material surfaces through a complex series of events, including the activation of platelets, leukocytes, complement, and the fibrinolytic system [11]. Thus it has long been thought that the suppression of protein adsorption is highly important in the design of blood-compatible surfaces. Nevertheless, even today, all blood-contacting devices cause thrombosis with long-term usage. In fact, synthetic vascular grafts with inside diameters of less than 6 mm cannot be used because they are prone to early thrombotic occlusion [12]. In the

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