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Modular polymer design to regulate phenotype and oxidative response of human coronary artery cells for potential stent coating applications

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ABSTRACT

Polymer properties can be tailored by copolymerizing subunits with specific physico-chemical characteristics. Vascular stent materials require biocompatibility, mechanical strength, and prevention of restenosis. Here we copolymerized poly(ε-caprolactone) (PCL), poly(ethylene glycol) (PEG), and carboxyl-PCL (cPCL) at varying molar ratios and characterized the resulting material properties. We then performed a short-term evaluation of these polymers for their applicability as potential coronary stent coating materials with two primary human coronary artery cell types: smooth muscle cells (HCASMC) and endothelial cells (HCAEC). Changes in proliferation and phenotype were dependent upon intracellular reactive oxygen species (ROS) levels, and 4%PEG–96%PCL–0%cPCL was identified as the most appropriate coating material for this application. After 3 days on this substrate HCASMC maintained a healthy contractile phenotype and HCAEC exhibited a physiologically relevant proliferation rate and a balanced redox state. Other test substrates promoted a pathological, synthetic phenotype of HCASMC and/or hyperproliferation of HCAEC. Phenotypic changes of HCASMC appeared to be modulated by the Young's modulus and surface charge of the test substrates, indicating a structure–function relationship that can be exploited for intricate control over vascular cell functions. These data indicate that tailored copolymer properties can direct vascular cell behavior and provide insights for further development of biologically instructive stent coating materials.

1. Introduction

The physico-chemical and mechanical properties of biomaterials modulate the response of the cells and tissues with which they interact [1–4]. In particular, polymers can be designed to control cell activity and fate through structure–function relationships [4]. Copolymerization techniques provide a means for tuning polymer properties by incorporating subunits with different characteristics and varying their molar ratios, thereby controlling micro and macro structures [4]. By understanding the effect of each subunit on the resulting polymer properties, as well as the ability of each subunit to modulate a cellular response, polymer properties can be precisely optimized to control a specific biological function.

Implantation of a vascular stent is crucial to reduce human morbidity and mortality resulting from vascular disease-induced localized blood flow constriction [5]. Current stent technologies include bare metal stents, polymers, and drug eluting stents (e.g. bare metal stents with a surface coating of polymers and drugs), yet each of these technologies poses a specific set of issues that has prevented its dominance of the clinical market. For example, bare metal stents are non-biodegradable and have been shown to cause restenosis, certain types of polymer stents can produce by-products that stimulate an inflammatory response, and drug eluting stents promote late thrombosis resulting from delayed re-endothelialization [5,6]. Therefore, much attention has recently been paid to design instructive, bioactive, and bioresorbable materials as a solution to the problems associated with classical treatments [7]. The ideal properties of a stent material include sufficient mechanical strength, moderate degradation kinetics, resorbable by-products, and regulation of cellular activities (i.e. proliferation and viability), each of which can be precisely controlled by understanding how the polymer chemistry affects the subsequent cellular response.

In order to design polymers for potential coronary stent coating applications, an insight into how these materials modulate the response of the cells with which they interact is of the utmost importance. The vasculature is primarily comprised of smooth muscle cells (SMC) and endothelial cells (EC). In general, healthy vascular SMC proliferate at a very low rate and assume a contractile phenotype that is characterized by smooth muscle myosin heavy chain (smMHC) expression, and a spindle-like morphology [8,9]. In contrast, unhealthy, "dedifferentiated" SMC assume a circular, cobble

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